Clinical trial results:
Open-Label, Randomized Trial of Nivolumab (BMS-936558) plus Pemetrexed/Platinum or Nivolumab plus Ipilimumab (BMS-734016) vs Pemetrexed plus Platinum in Stage IV or Recurrent Non-Small Cell Lung Cancer (NSCLC) Subjects with Epidermal Growth Factor Receptor (EGFR) Mutation Who Failed 1L or 2L EGFR Tyrosine Kinase Inhibitor Therapy: CheckMate 722: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 722.

Summary

EudraCT number	2017-002672-38
Trial protocol	ES
Global end of trial date	17 October 2022

Results information

Result version number	v1 (current)
This version publication date	22 September 2023
First version publication date	22 September 2023

Trial information

Trial identification

Sponsor protocol code	CA209-722

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	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.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the PFS by BICR of nivolumab plus pemetrexed/platinum to pemetrexed plus platinum in EGFR mutation positive (ie, G719X, L861Q, Del 19, and L858R), metastatic or recurrent NSCLC that has progressed on 1L or 2L EGFR TKI.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 54
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Hong Kong: 8
Country: Number of subjects enrolled	Japan: 100
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 91
Country: Number of subjects enrolled	Singapore: 13
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Taiwan: 74
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	367
EEA total number of subjects	24

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)	211
From 65 to 84 years	155
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

367 participants were randomized; 355 participants were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivolumab plus Platinum-doublet Chemotherapy

Arm description:

Nivolumab was administered IV every 3 weeks with platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) IV for a maximum of 4 cycles. Treatment administered was either Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Following completion of the fourth cycle of nivolumab/chemotherapy, all participants who did not experience disease progression should have continued nivolumab 360 mg IV and pemetrexed (500 mg/m2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, whichever comes first. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	BMS-936558-01
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

360 mg IV every 3 weeks for a maximum of 4 cycles

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate, Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m2 on Day 1 of each Cycle

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

Dosage and administration details:

75 mg/m2 administered on Day 1 of each cycle

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

AUC 5 or 6 administered on Day 1 of each cycle

Arm title	Arm B: Nivolumab plus Ipilimumab

Arm description:

Nivolumab 3 mg/kg IV was administered every 2 weeks and ipilimumab 1 mg/kg IV was administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

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

Dosage and administration details:

1 mg/kg IV every 6 weeks for a maximum of 24 months

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	BMS-936558-01
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

360 mg IV every 3 weeks for a maximum of 4 cycles

Arm title	Arm C: Platinum Doublet Chemotherapy

Arm description:

Platinum-doublet chemotherapy (investigator’s choice of cisplatin or carboplatin) was administered IV in 3-week cycles for up to a maximum of 4 cycles. Participants received either Pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Platinum-doublet chemotherapy continued until disease progression, unacceptable toxicity, or completion of the 4 cycles, whichever came first. Participants who had stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should have continued pemetrexed alone as maintenance therapy until disease progression, or unacceptable toxicity.

Arm type	Active comparator
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate, Concentrate and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m2 on Day 1 of each Cycle

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

Dosage and administration details:

AUC 5 or 6 administered on Day 1 of each cycle

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75 mg/m2 administered on Day 1 of each cycle

Number of subjects in period 1	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy
Started	144	73	150
Completed	141	71	143
Not completed	3	2	7
Withdrawal by Participant	-	-	4
Other Reasons	-	1	1
Adverse Event Unrelated to Study drug	1	-	-
Participant no Longer Meets Study Criteria	2	1	2

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivolumab plus Platinum-doublet Chemotherapy

Arm description:

Nivolumab was administered IV every 3 weeks with platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) IV for a maximum of 4 cycles. Treatment administered was either Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Following completion of the fourth cycle of nivolumab/chemotherapy, all participants who did not experience disease progression should have continued nivolumab 360 mg IV and pemetrexed (500 mg/m2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, whichever comes first. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	BMS-936558-01
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details: 360 mg IV every 3 weeks for a maximum of 4 cycles	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: AUC 5 or 6 administered on Day 1 of each cycle	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m2 administered on Day 1 of each cycle	
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate, Concentrate and solvent for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 500 mg/m2 on Day 1 of each Cycle	
Arm title	Arm B: Nivolumab plus Ipilimumab

Arm description:

Nivolumab 3 mg/kg IV was administered every 2 weeks and ipilimumab 1 mg/kg IV was administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 1 mg/kg IV every 6 weeks for a maximum of 24 months	
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	BMS-936558-01
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 360 mg IV every 3 weeks for a maximum of 4 cycles	
Arm title	Arm C: Platinum Doublet Chemotherapy

Arm description:

Platinum-doublet chemotherapy (investigator’s choice of cisplatin or carboplatin) was administered IV in 3-week cycles for up to a maximum of 4 cycles. Participants received either Pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Platinum-doublet chemotherapy continued until disease progression, unacceptable toxicity, or completion of the 4 cycles, whichever came first. Participants who had stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should have continued pemetrexed alone as maintenance therapy until disease progression, or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate, Concentrate and solvent for solution for injection
Routes of administration	Intravenous use
Dosage and administration details: 500 mg/m2 on Day 1 of each Cycle	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: AUC 5 or 6 administered on Day 1 of each cycle	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 75 mg/m2 administered on Day 1 of each cycle	

Number of subjects in period 2	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy
Started	141	71	143
Completed	3	5	0
Not completed	138	66	143
Adverse event, serious fatal	-	2	3
Withdrawal by Participant	8	5	13
Other Reasons	1	1	4
Participant Req to Discontinue Study Treatment	8	-	5
Maximum Clinical Benefit	1	-	1
Study Drug Toxicity	9	4	10
Adverse Event Unrelated to Study drug	1	1	6
Participant no Longer Meets Study Criteria	-	1	-
Disease Progression	109	52	101
Administrative Reason by Sponsor	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Arm A: Nivolumab plus Platinum-doublet Chemotherapy

Reporting group description:

Nivolumab was administered IV every 3 weeks with platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) IV for a maximum of 4 cycles. Treatment administered was either Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Following completion of the fourth cycle of nivolumab/chemotherapy, all participants who did not experience disease progression should have continued nivolumab 360 mg IV and pemetrexed (500 mg/m2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, whichever comes first. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Reporting group title	Arm B: Nivolumab plus Ipilimumab

Reporting group description:

Nivolumab 3 mg/kg IV was administered every 2 weeks and ipilimumab 1 mg/kg IV was administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

Reporting group title	Arm C: Platinum Doublet Chemotherapy

Reporting group description:

Platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) was administered IV in 3-week cycles for up to a maximum of 4 cycles. Participants received either Pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Platinum-doublet chemotherapy continued until disease progression, unacceptable toxicity, or completion of the 4 cycles, whichever came first. Participants who had stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should have continued pemetrexed alone as maintenance therapy until disease progression, or unacceptable toxicity.

Reporting group values	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy
Number of subjects	144	73	150
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	75	44	92
From 65-84 years	69	29	57
85 years and over	0	0	1
Age Continuous Units: Years			
arithmetic mean	62.3	61.9	60.7
standard deviation	± 10.6	± 10.6	± 10.1
Sex: Female, Male Units: Participants			
Female	83	37	94

Male	61	36	56

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	136	68	139
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	7	3	11
More than one race	0	0	0
Unknown or Not Reported	1	2	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	59	39	73
Unknown or Not Reported	85	34	77

Reporting group values	Total		
Number of subjects	367		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	211		
From 65-84 years	155		
85 years and over	1		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	214		
Male	153		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	343		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	21		
More than one race	0		
Unknown or Not Reported	3		

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	171		
Unknown or Not Reported	196		

End points

End points reporting groups

Reporting group title	Arm A: Nivolumab plus Platinum-doublet Chemotherapy

Reporting group description:

Nivolumab was administered IV every 3 weeks with platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) IV for a maximum of 4 cycles. Treatment administered was either Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Following completion of the fourth cycle of nivolumab/chemotherapy, all participants who did not experience disease progression should have continued nivolumab 360 mg IV and pemetrexed (500 mg/m2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, whichever comes first. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Reporting group title	Arm B: Nivolumab plus Ipilimumab

Reporting group description:

Nivolumab 3 mg/kg IV was administered every 2 weeks and ipilimumab 1 mg/kg IV was administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

Reporting group title	Arm C: Platinum Doublet Chemotherapy

Reporting group description:

Platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) was administered IV in 3-week cycles for up to a maximum of 4 cycles. Participants received either Pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Platinum-doublet chemotherapy continued until disease progression, unacceptable toxicity, or completion of the 4 cycles, whichever came first. Participants who had stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should have continued pemetrexed alone as maintenance therapy until disease progression, or unacceptable toxicity.

Reporting group title	Arm A: Nivolumab plus Platinum-doublet Chemotherapy

Reporting group description:

Nivolumab was administered IV every 3 weeks with platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) IV for a maximum of 4 cycles. Treatment administered was either Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Following completion of the fourth cycle of nivolumab/chemotherapy, all participants who did not experience disease progression should have continued nivolumab 360 mg IV and pemetrexed (500 mg/m2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, whichever comes first. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Reporting group title	Arm B: Nivolumab plus Ipilimumab

Reporting group description:

Nivolumab 3 mg/kg IV was administered every 2 weeks and ipilimumab 1 mg/kg IV was administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

Reporting group title	Arm C: Platinum Doublet Chemotherapy

Reporting group description:

Platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) was administered IV in 3-week cycles for up to a maximum of 4 cycles. Participants received either Pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Platinum-doublet chemotherapy continued until disease progression, unacceptable toxicity, or completion of the 4 cycles, whichever came first. Participants who had stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should have continued pemetrexed alone as maintenance therapy until disease progression, or unacceptable toxicity.

Primary: Progression Free Survival (PFS) by Blinded Independent Centralized Review (BICR)

End point title	Progression Free Survival (PFS) by Blinded Independent Centralized Review (BICR)

End point description:

PFS is defined as the time between the date of randomization and the date of first documented tumor progression, as determined by BICR (per RECIST v1.1 criteria), or death due to any cause, whichever occurs first.
Participants who died without reported progression will be considered to have progressed on the date of their death. Subsequent therapy was accounted for by censoring at the last evaluable tumor assessment on or prior to the date of subsequent therapy.
Progression is the appearance of one or more new lesions.
RECIST - "response evaluation criteria in solid tumors" is a standard system to measure tumor response to treatment.
Based on Kaplan-Meier estimates

End point type	Primary

End point timeframe:

From randomization to the date of first documented tumor progression or death (approximately 58 months)

End point values	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	73	150	
Units: Months				
median (confidence interval 95%)	5.59 (4.47 to 6.80)	1.54 (1.41 to 2.63)	5.45 (4.40 to 5.65)	

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Arm B: Nivolumab plus Ipilimumab v Arm C: Platinum Doublet Chemotherapy
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.43
upper limit	2.99

Statistical analysis title	Hazard Ratio
Comparison groups	Arm A: Nivolumab plus Platinum-doublet Chemotherapy v Arm

	C: Platinum Doublet Chemotherapy
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0528 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1

Notes:

[1] - Log-rank test stratified by PD-L1 expression (>= 1% vs <1%/indeterminate/not evaluable), brain metastases (presence
vs absence), smoking history (current/former vs never smoker), and prior osimertinib use (yes vs no) from IRT.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a participant was known to be alive.
Median based on Kaplan-Meier Estimates

End point type	Secondary

End point timeframe:

From randomization to the date of death due to any cause (up to approximately 67 months)

End point values	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	73	150	
Units: Months				
median (confidence interval 95%)	19.35 (16.13 to 20.99)	17.12 (13.67 to 23.59)	15.90 (14.00 to 18.79)	

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Arm B: Nivolumab plus Ipilimumab v Arm C: Platinum Doublet Chemotherapy

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.52

Statistical analysis title	Hazard Ratio
Comparison groups	Arm A: Nivolumab plus Platinum-doublet Chemotherapy v Arm C: Platinum Doublet Chemotherapy
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.218
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.12

Secondary: Objective Response Rate (ORR) by Blinded Independent Centralized Review (BICR)

End point title	Objective Response Rate (ORR) by Blinded Independent Centralized Review (BICR)

End point description:

ORR is number of randomized participants who have confirmed best overall response (BOR) of complete response (CR) or partial response (PR) using RECIST v1.1 criteria by BICR assessment.
BOR is the best response designation, between randomization and objectively documented progression per RECIST v1.1 criteria by BICR or the date of subsequent anti-cancer therapy, whichever occurs first.
PR is at least a 30% decrease in the sum of diameters of target lesions, using the baseline sum diameters as reference. CR is disappearance of all target lesions and a reduction in the short axis of pathological lymph nodes to <10 mm (whether target or non-target).
Radiographic tumor response assessments from Week 7 (± 7 days), then every 6 weeks (± 7 days) until Week 49 and every 12 weeks (± 7 days) thereafter, until disease progression, treatment discontinued, or the start of subsequent anti-cancer therapy.
CR+PR, confidence interval based on the Clopper and Pearson method.

End point type	Secondary

End point timeframe:

From randomization to the date of objectively documented progression, date of death, or the date of subsequent therapy (up to approximately 67 months)

End point values	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	73	150	
Units: Percent of Participants				
number (confidence interval 95%)	30.6 (23.2 to 38.8)	13.7 (6.8 to 23.8)	26.7 (19.8 to 34.5)	

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Arm A: Nivolumab plus Platinum-doublet Chemotherapy v Arm C: Platinum Doublet Chemotherapy
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.16

Secondary: 12 Month Progression Free Survival Rates (PFSR) by Blinded Independent Centralized Review (BICR)

End point title	12 Month Progression Free Survival Rates (PFSR) by Blinded Independent Centralized Review (BICR)

End point description:

The PFSR at 12 months is defined as the percent of treated participants remaining progression free and surviving at 12 months since the first dosing date. Progression is the appearance of one or more new lesions. Point estimates are derived from Kaplan-Meier analyses.

End point type	Secondary

End point timeframe:

12 Months after first treatment dose

End point values	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	73	150	
Units: Percent of Participants				
number (confidence interval 95%)	21.2 (14.3 to 29.1)	12.2 (5.5 to 21.7)	15.9 (9.3 to 24.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by Blinded Independent Centralized Review (BICR)

End point title	Duration of Response (DOR) by Blinded Independent Centralized Review (BICR)

End point description:

DOR is the time between first response (CR or PR) and first documented disease progression as determined by Response Evaluation Criteria In Solid Tumors (RECIST 1.1) or death due to any cause (death occurring after re-treatment or randomization to new combination treatment not included), whichever occurred first.
PR is at least a 30% decrease in the sum of diameters of target lesions, using baseline sum diameters as reference. CR is disappearance of all target lesions and a reduction in the short axis of pathological lymph nodes to <10 mm (target or non-target).
Radiographic tumor response assessments from Week 7 (± 7 days), then every 6 weeks (± 7 days) until Week 49 and every 12 weeks (± 7 days) thereafter, until disease progression, treatment discontinued, or the start of subsequent anti-cancer therapy.
Participants who neither progress nor die were censored on the date of their last assessment.
99999 = Not Available/ Not Applicable
Median computed using Kaplan-Meier method

End point type	Secondary

End point timeframe:

From randomization to the date of first documented disease progression or death due to any cause (approximately 67 months)

End point values	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	10	40	
Units: Months				
median (confidence interval 95%)	6.67 (4.17 to 12.45)	50.04 (2.86 to 99999)	5.55 (4.07 to 9.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: 9 Month Progression Free Survival Rates (PFSR) by Blinded Independent Centralized Review (BICR)

End point title	9 Month Progression Free Survival Rates (PFSR) by Blinded Independent Centralized Review (BICR)

End point description:

The PFSR at 9 months is defined as the percent of treated participants remaining progression free and surviving at 9 months since the first dosing date. Progression is the appearance of one or more new lesions.
Point estimates are derived from Kaplan-Meier analyses.

End point type	Secondary

End point timeframe:

9 months after first treatment dose

End point values	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab	Arm C: Platinum Doublet Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	73	150	
Units: Percent of Participants				
number (confidence interval 95%)	25.9 (18.4 to 34.0)	12.2 (5.5 to 21.7)	19.8 (12.6 to 28.1)	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events (SAEs) and Non-Serious Adverse Events (NSAEs) was assessed from first dose to 100 days post the last dose of study therapy (up to approximately an average of 11 months and a maximum of 51 months).

Adverse event reporting additional description:

The number at risk for SAEs and NSAEs represents all participants that received at least 1 dose of study therapy or similar.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Arm A: Nivolumab plus Platinum-doublet Chemotherapy

Reporting group description:

Nivolumab was administered IV every 3 weeks with platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) IV for a maximum of 4 cycles. Treatment administered was either Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Nivolumab 360 mg IV, followed by pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Following completion of the fourth cycle of nivolumab/chemotherapy, all participants who did not experience disease progression should have continued nivolumab 360 mg IV and pemetrexed (500 mg/m2) every 3 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, or study closure, whichever comes first. Nivolumab should only be administered for a maximum of 24 months (96 weeks) from the first study treatment.

Reporting group title	Arm C: Platinum Doublet Chemotherapy

Reporting group description:

Platinum-doublet chemotherapy (investigator's choice of cisplatin or carboplatin) was administered IV in 3-week cycles for up to a maximum of 4 cycles. Participants received either Pemetrexed (500 mg/m2) with cisplatin (75 mg/m2) administered on Day 1 of each cycle OR Pemetrexed (500 mg/m2) with carboplatin (AUC 5 or 6) administered on Day 1 of each cycle. Platinum-doublet chemotherapy continued until disease progression, unacceptable toxicity, or completion of the 4 cycles, whichever came first. Participants who had stable disease or response after 4 cycles of pemetrexed with cisplatin or carboplatin should have continued pemetrexed alone as maintenance therapy until disease progression, or unacceptable toxicity.

Reporting group title	Arm B: Nivolumab plus Ipilimumab

Reporting group description:

Nivolumab 3 mg/kg IV was administered every 2 weeks and ipilimumab 1 mg/kg IV was administered every 6 weeks until the progression of disease, discontinuation due to toxicity, withdrawal of consent, a maximum of 24 months (96 weeks) from the first study treatment, or study closure.

Serious adverse events	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm C: Platinum Doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 141 (54.61%)	55 / 143 (38.46%)	46 / 71 (64.79%)
number of deaths (all causes)	91	104	55
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Cancer pain			
subjects affected / exposed	2 / 141 (1.42%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Brain cancer metastatic			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Plasma cell myeloma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Non-small cell lung cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Neoplasm progression			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Metastases to meninges			

subjects affected / exposed	0 / 141 (0.00%)	2 / 143 (1.40%)	0 / 71 (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
Renal cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Metastases to bone			
subjects affected / exposed	0 / 141 (0.00%)	2 / 143 (1.40%)	0 / 71 (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
Malignant pleural effusion			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	25 / 141 (17.73%)	22 / 143 (15.38%)	20 / 71 (28.17%)
occurrences causally related to treatment / all	0 / 27	0 / 29	0 / 22
deaths causally related to treatment / all	0 / 12	0 / 12	0 / 10
Malignant ascites			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Metastases to central nervous system			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumour pain			
subjects affected / exposed	2 / 141 (1.42%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumour associated fever			

subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Transitional cell carcinoma			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 141 (2.13%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Peripheral venous disease			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
General disorders and administration site conditions			
Catheter site oedema			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Asthenia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Fatigue			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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

Pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Pyrexia			
subjects affected / exposed	3 / 141 (2.13%)	1 / 143 (0.70%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sudden death			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Swelling			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Dyspnoea			
subjects affected / exposed	0 / 141 (0.00%)	2 / 143 (1.40%)	5 / 71 (7.04%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Interstitial lung disease			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 141 (0.71%)	3 / 143 (2.10%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	5 / 141 (3.55%)	1 / 143 (0.70%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	6 / 6	1 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Depression			

subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Delirium			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
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 creatine increased			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Liver function test increased			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 141 (0.00%)	2 / 143 (1.40%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Femoral neck fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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 discharge			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			

subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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 fracture			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Fall			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Wrist fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Atrial fibrillation			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Pericardial effusion			

subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prinzmetal angina			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Sinus bradycardia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Immune-mediated myocarditis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Cervical cord compression			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Optic neuritis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Ischaemic stroke			

subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Intracranial pressure increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Hydrocephalus			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 141 (0.71%)	3 / 143 (2.10%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Febrile neutropenia			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelosuppression			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	0 / 71 (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
Leukocytosis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Pancytopenia			

subjects affected / exposed	2 / 141 (1.42%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Colitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Diarrhoea			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Inguinal hernia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Nausea			
subjects affected / exposed	3 / 141 (2.13%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 141 (2.84%)	1 / 143 (0.70%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	4 / 5	1 / 1	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	3 / 141 (2.13%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	2 / 141 (1.42%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			

subjects affected / exposed	2 / 141 (1.42%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticarial vasculitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 141 (1.42%)	1 / 143 (0.70%)	0 / 71 (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
Nephrolithiasis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Pyelocaliectasis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Hypopituitarism			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis subacute			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Tenosynovitis stenosans			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated myositis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Infections and infestations			
Carbuncle			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Atypical pneumonia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Breast cellulitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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

Cellulitis			
subjects affected / exposed	3 / 141 (2.13%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Herpes zoster			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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 influenzal			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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	0 / 141 (0.00%)	0 / 143 (0.00%)	2 / 71 (2.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Pneumonia			
subjects affected / exposed	10 / 141 (7.09%)	7 / 143 (4.90%)	4 / 71 (5.63%)
occurrences causally related to treatment / all	3 / 10	1 / 7	1 / 4
deaths causally related to treatment / all	1 / 4	1 / 3	0 / 1
Pneumonia aspiration			
subjects affected / exposed	2 / 141 (1.42%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Pneumonia klebsiella			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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 infection			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Tuberculosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 143 (0.70%)	0 / 71 (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
Urinary tract infection			

subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 143 (0.00%)	0 / 71 (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
Decreased appetite			
subjects affected / exposed	4 / 141 (2.84%)	0 / 143 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 141 (0.00%)	0 / 143 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Arm A: Nivolumab plus Platinum-doublet Chemotherapy	Arm C: Platinum Doublet Chemotherapy	Arm B: Nivolumab plus Ipilimumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	136 / 141 (96.45%)	140 / 143 (97.90%)	62 / 71 (87.32%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	4 / 141 (2.84%)	3 / 143 (2.10%)	7 / 71 (9.86%)
occurrences (all)	4	3	7
Malignant neoplasm progression			
subjects affected / exposed	1 / 141 (0.71%)	1 / 143 (0.70%)	4 / 71 (5.63%)
occurrences (all)	2	1	4

Cancer pain			
subjects affected / exposed	9 / 141 (6.38%)	9 / 143 (6.29%)	5 / 71 (7.04%)
occurrences (all)	9	9	5
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 141 (6.38%)	4 / 143 (2.80%)	5 / 71 (7.04%)
occurrences (all)	13	4	5
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	8 / 141 (5.67%)	9 / 143 (6.29%)	0 / 71 (0.00%)
occurrences (all)	10	9	0
Malaise			
subjects affected / exposed	18 / 141 (12.77%)	21 / 143 (14.69%)	5 / 71 (7.04%)
occurrences (all)	24	25	6
Fatigue			
subjects affected / exposed	30 / 141 (21.28%)	19 / 143 (13.29%)	15 / 71 (21.13%)
occurrences (all)	69	26	17
Asthenia			
subjects affected / exposed	12 / 141 (8.51%)	10 / 143 (6.99%)	3 / 71 (4.23%)
occurrences (all)	20	11	3
Pyrexia			
subjects affected / exposed	29 / 141 (20.57%)	17 / 143 (11.89%)	14 / 71 (19.72%)
occurrences (all)	38	18	19
Oedema peripheral			
subjects affected / exposed	26 / 141 (18.44%)	18 / 143 (12.59%)	8 / 71 (11.27%)
occurrences (all)	30	20	8
Non-cardiac chest pain			
subjects affected / exposed	10 / 141 (7.09%)	8 / 143 (5.59%)	7 / 71 (9.86%)
occurrences (all)	10	8	8
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 141 (11.35%)	18 / 143 (12.59%)	16 / 71 (22.54%)
occurrences (all)	17	18	17
Productive cough			
subjects affected / exposed	9 / 141 (6.38%)	11 / 143 (7.69%)	8 / 71 (11.27%)
occurrences (all)	15	12	8

Hiccups			
subjects affected / exposed	12 / 141 (8.51%)	8 / 143 (5.59%)	2 / 71 (2.82%)
occurrences (all)	16	13	3
Haemoptysis			
subjects affected / exposed	9 / 141 (6.38%)	9 / 143 (6.29%)	4 / 71 (5.63%)
occurrences (all)	9	10	4
Dyspnoea			
subjects affected / exposed	15 / 141 (10.64%)	12 / 143 (8.39%)	14 / 71 (19.72%)
occurrences (all)	18	13	16
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 141 (12.06%)	22 / 143 (15.38%)	6 / 71 (8.45%)
occurrences (all)	18	25	6
Anxiety			
subjects affected / exposed	6 / 141 (4.26%)	3 / 143 (2.10%)	4 / 71 (5.63%)
occurrences (all)	7	3	4
Investigations			
Neutrophil count decreased			
subjects affected / exposed	42 / 141 (29.79%)	45 / 143 (31.47%)	4 / 71 (5.63%)
occurrences (all)	118	117	6
Blood creatinine increased			
subjects affected / exposed	19 / 141 (13.48%)	15 / 143 (10.49%)	1 / 71 (1.41%)
occurrences (all)	27	23	2
Aspartate aminotransferase increased			
subjects affected / exposed	35 / 141 (24.82%)	27 / 143 (18.88%)	11 / 71 (15.49%)
occurrences (all)	87	39	12
Amylase increased			
subjects affected / exposed	13 / 141 (9.22%)	9 / 143 (6.29%)	3 / 71 (4.23%)
occurrences (all)	23	13	3
Alanine aminotransferase increased			
subjects affected / exposed	35 / 141 (24.82%)	26 / 143 (18.18%)	12 / 71 (16.90%)
occurrences (all)	83	41	16
Platelet count decreased			
subjects affected / exposed	19 / 141 (13.48%)	28 / 143 (19.58%)	6 / 71 (8.45%)
occurrences (all)	45	50	7
Weight decreased			

subjects affected / exposed	9 / 141 (6.38%)	6 / 143 (4.20%)	7 / 71 (9.86%)
occurrences (all)	10	6	7
White blood cell count decreased			
subjects affected / exposed	38 / 141 (26.95%)	35 / 143 (24.48%)	3 / 71 (4.23%)
occurrences (all)	129	95	6
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 141 (15.60%)	19 / 143 (13.29%)	5 / 71 (7.04%)
occurrences (all)	25	23	5
Dysgeusia			
subjects affected / exposed	9 / 141 (6.38%)	10 / 143 (6.99%)	1 / 71 (1.41%)
occurrences (all)	13	11	1
Dizziness			
subjects affected / exposed	15 / 141 (10.64%)	14 / 143 (9.79%)	7 / 71 (9.86%)
occurrences (all)	21	14	7
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	10 / 141 (7.09%)	6 / 143 (4.20%)	1 / 71 (1.41%)
occurrences (all)	32	9	1
Neutropenia			
subjects affected / exposed	22 / 141 (15.60%)	6 / 143 (4.20%)	3 / 71 (4.23%)
occurrences (all)	110	7	5
Anaemia			
subjects affected / exposed	66 / 141 (46.81%)	58 / 143 (40.56%)	7 / 71 (9.86%)
occurrences (all)	115	77	8
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	35 / 141 (24.82%)	21 / 143 (14.69%)	7 / 71 (9.86%)
occurrences (all)	51	35	10
Stomatitis			
subjects affected / exposed	12 / 141 (8.51%)	10 / 143 (6.99%)	4 / 71 (5.63%)
occurrences (all)	14	12	4
Nausea			
subjects affected / exposed	63 / 141 (44.68%)	60 / 143 (41.96%)	12 / 71 (16.90%)
occurrences (all)	104	98	15
Diarrhoea			

subjects affected / exposed	18 / 141 (12.77%)	17 / 143 (11.89%)	17 / 71 (23.94%)
occurrences (all)	23	19	25
Constipation			
subjects affected / exposed	52 / 141 (36.88%)	57 / 143 (39.86%)	21 / 71 (29.58%)
occurrences (all)	66	82	32
Abdominal pain upper			
subjects affected / exposed	3 / 141 (2.13%)	4 / 143 (2.80%)	4 / 71 (5.63%)
occurrences (all)	3	5	4
Abdominal pain			
subjects affected / exposed	3 / 141 (2.13%)	11 / 143 (7.69%)	5 / 71 (7.04%)
occurrences (all)	3	11	8
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	12 / 141 (8.51%)	1 / 143 (0.70%)	9 / 71 (12.68%)
occurrences (all)	12	2	15
Rash			
subjects affected / exposed	2 / 141 (1.42%)	0 / 143 (0.00%)	9 / 71 (12.68%)
occurrences (all)	3	0	10
Pruritus			
subjects affected / exposed	17 / 141 (12.06%)	8 / 143 (5.59%)	18 / 71 (25.35%)
occurrences (all)	22	9	25
Eczema			
subjects affected / exposed	2 / 141 (1.42%)	1 / 143 (0.70%)	5 / 71 (7.04%)
occurrences (all)	2	1	5
Alopecia			
subjects affected / exposed	6 / 141 (4.26%)	8 / 143 (5.59%)	4 / 71 (5.63%)
occurrences (all)	6	8	4
Rash maculo-papular			
subjects affected / exposed	9 / 141 (6.38%)	4 / 143 (2.80%)	2 / 71 (2.82%)
occurrences (all)	9	4	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	15 / 141 (10.64%)	0 / 143 (0.00%)	12 / 71 (16.90%)
occurrences (all)	16	0	12
Hyperthyroidism			

subjects affected / exposed	7 / 141 (4.96%)	0 / 143 (0.00%)	8 / 71 (11.27%)
occurrences (all)	8	0	8
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 141 (4.26%)	3 / 143 (2.10%)	5 / 71 (7.04%)
occurrences (all)	7	3	6
Arthralgia			
subjects affected / exposed	15 / 141 (10.64%)	10 / 143 (6.99%)	9 / 71 (12.68%)
occurrences (all)	17	10	11
Back pain			
subjects affected / exposed	21 / 141 (14.89%)	12 / 143 (8.39%)	5 / 71 (7.04%)
occurrences (all)	26	12	5
Muscular weakness			
subjects affected / exposed	7 / 141 (4.96%)	3 / 143 (2.10%)	4 / 71 (5.63%)
occurrences (all)	8	3	4
Myalgia			
subjects affected / exposed	6 / 141 (4.26%)	4 / 143 (2.80%)	6 / 71 (8.45%)
occurrences (all)	9	5	7
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 141 (3.55%)	3 / 143 (2.10%)	4 / 71 (5.63%)
occurrences (all)	5	5	4
Upper respiratory tract infection			
subjects affected / exposed	9 / 141 (6.38%)	9 / 143 (6.29%)	6 / 71 (8.45%)
occurrences (all)	11	10	8
Pneumonia			
subjects affected / exposed	7 / 141 (4.96%)	7 / 143 (4.90%)	5 / 71 (7.04%)
occurrences (all)	8	7	5
Paronychia			
subjects affected / exposed	6 / 141 (4.26%)	1 / 143 (0.70%)	4 / 71 (5.63%)
occurrences (all)	7	1	4
Nasopharyngitis			
subjects affected / exposed	8 / 141 (5.67%)	1 / 143 (0.70%)	1 / 71 (1.41%)
occurrences (all)	9	1	2
Conjunctivitis			

subjects affected / exposed	10 / 141 (7.09%)	2 / 143 (1.40%)	2 / 71 (2.82%)
occurrences (all)	10	2	6
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	42 / 141 (29.79%)	52 / 143 (36.36%)	16 / 71 (22.54%)
occurrences (all)	83	68	23
Hypoalbuminaemia			
subjects affected / exposed	9 / 141 (6.38%)	6 / 143 (4.20%)	2 / 71 (2.82%)
occurrences (all)	18	6	4
Hypokalaemia			
subjects affected / exposed	11 / 141 (7.80%)	6 / 143 (4.20%)	6 / 71 (8.45%)
occurrences (all)	14	6	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2018	Stopped enrollment to Arm B (nivolumab + ipilimumab)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported