



Clinical trial results: CheckpOiNt blockade For Inhibition of Relapsed Mesothelioma (CONFIRM): A Phase III Trial to Evaluate the Efficacy of Nivolumab in Relapsed Mesothelioma Summary

EudraCT number	2016-003111-35
Trial protocol	GB
Global end of trial date	16 February 2022

Results information

Result version number	v1 (current)
This version publication date	01 March 2023
First version publication date	01 March 2023

Trial information

Trial identification

Sponsor protocol code	22864
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Additional study identifiers

ISRCTN number	ISRCTN79814141
ClinicalTrials.gov id (NCT number)	NCT03063450
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Southampton
Sponsor organisation address	University Road, Southampton, United Kingdom, SO17 1BJ
Public contact	Calley Middleton, University of Southampton , 44 02381205608, C.Middleton@soton.ac.uk
Scientific contact	Calley Middleton, University of Southampton , 44 02381205608, C.Middleton@soton.ac.uk

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	09 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 February 2022
Global end of trial reached?	Yes
Global end of trial date	16 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial aims to determine whether nivolumab increases overall survival in patients with relapsed mesothelioma.

Protection of trial subjects:

Nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level. Adverse events have been broadly consistent across tumour types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put subjects at increased risk.

Trial participants were frequently monitored for adverse events, and participants and their treating clinicians are able to withdraw treatment as desired.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 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	United Kingdom: 332
Worldwide total number of subjects	332
EEA total number of subjects	0

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)	81
From 65 to 84 years	251
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients underwent screening evaluations (e.g., medical history, physical exam, CT scan), within 28 days prior to first trial treatment, to determine eligibility. Concomitant medications were assessed within 14 days. Pregnancy tests were completed for women of child-bearing potential at screening, within 24 hours prior to start of treatment.

Period 1

Period 1 title	Final analysis (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Treatment allocation was achieved through use of an online randomisation system. Blinding was achieved by ensuring only pharmacy staff were aware of participant allocation, and through the use of placebo (matched on volume and delivery).

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

240mg over 30 minutes every 14 days (+/-2 days). The infusion was to be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

240mg over 30 minutes every 14 days (+/-2 days). The infusion was to be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm.

Number of subjects in period 1	Nivolumab	Placebo
Started	221	111
Completed	13	5
Not completed	208	106
Consent withdrawn by subject	7	4
Physician decision	8	3
Disease progression	142	85
Adverse event, non-fatal	30	3
Other	21	11

Baseline characteristics

Reporting groups

Reporting group title	Nivolumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Nivolumab	Placebo	Total
Number of subjects	221	111	332
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	70	71	
inter-quartile range (Q1-Q3)	65 to 74	65 to 76	-
Gender categorical Units: Subjects			
Female	54	25	79
Male	167	86	253

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Analysed as randomised	

Reporting group values	ITT		
Number of subjects	332		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			

Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	70		
inter-quartile range (Q1-Q3)	65 to 75		
Gender categorical			
Units: Subjects			
Female	79		
Male	253		

End points

End points reporting groups

Reporting group title	Nivolumab
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Analysed as randomised	

Primary: Overall survival

End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe:	
From randomisation to at least 6 months after the last participant was recruited	

End point values	Nivolumab	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	221	111	332	
Units: Months				
median (confidence interval 95%)	9.5 (7.7 to 11.0)	6.8 (5.0 to 7.9)	8.0 (7.2 to 9.5)	

Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	Nivolumab v Placebo v ITT
Number of subjects included in analysis	664
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.04
Variability estimate	Standard error of the mean
Dispersion value	0.58

Primary: Progression free survival

End point title	Progression free survival
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End point description:

End point type	Primary
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End point timeframe:

From randomisation until at least 6 months after last participant is recruited

End point values	Nivolumab	Placebo	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	221	111	332	
Units: Months				
median (confidence interval 95%)	2.9 (2.8 to 4.1)	1.6 (1.4 to 2.6)	2.8 (2.7 to 2.9)	

Statistical analyses

Statistical analysis title	PFS
Comparison groups	Nivolumab v Placebo v ITT
Number of subjects included in analysis	664
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	0.08

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Nivolumab
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Nivolumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 221 (39.82%)	48 / 111 (43.24%)	
number of deaths (all causes)	198	100	
number of deaths resulting from adverse events	5	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous Cell Carcinoma Of Lung	Additional description: Squamous Cell Carcinoma Of Lung		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Neoplasm	Additional description: Bladder Neoplasm		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma Malignant	Additional description: Mesothelioma Malignant		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mesothelioma	Additional description: Mesothelioma		

subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis	Additional description: Deep Vein Thrombosis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abdominal Cavity Drainage	Additional description: Abdominal Cavity Drainage		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain Management	Additional description: Pain Management		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain	Additional description: Pain		
subjects affected / exposed	3 / 221 (1.36%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	1 / 221 (0.45%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise	Additional description: Malaise		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema Peripheral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Oedema Peripheral		
	0 / 221 (0.00%)	1 / 111 (0.90%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
General Physical Health Deterioration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: General Physical Health Deterioration		
	2 / 221 (0.90%)	0 / 111 (0.00%)	
	0 / 2	0 / 0	
	0 / 1	0 / 0	
Fatigue subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Fatigue		
	0 / 221 (0.00%)	1 / 111 (0.90%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Disease Progression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Disease Progression		
	0 / 221 (0.00%)	3 / 111 (2.70%)	
	0 / 0	0 / 3	
	0 / 0	0 / 2	
Chest Pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Chest Pain		
	1 / 221 (0.45%)	1 / 111 (0.90%)	
	0 / 1	0 / 1	
	0 / 0	0 / 0	
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Prostatitis		
	0 / 221 (0.00%)	1 / 111 (0.90%)	
	0 / 0	1 / 1	
	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders Pneumonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pneumonitis		
	2 / 221 (0.90%)	1 / 111 (0.90%)	
	2 / 2	1 / 1	
	0 / 0	0 / 0	
Respiratory Obstruction Unspecified	Additional description: Respiratory Obstruction Unspecified		

subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion	Additional description: Pleural Effusion		
subjects affected / exposed	3 / 221 (1.36%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration	Additional description: Pneumonia Aspiration		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism	Additional description: Pulmonary Embolism		
subjects affected / exposed	2 / 221 (0.90%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	18 / 221 (8.14%)	9 / 111 (8.11%)	
occurrences causally related to treatment / all	4 / 20	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Painful Respiration	Additional description: Painful Respiration		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Oedema	Additional description: Pulmonary Oedema		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional State	Additional description: Confusional State		

subjects affected / exposed	2 / 221 (0.90%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Bilirubin Increased	Additional description: Blood Bilirubin Increased		
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-Glutamyltransferase Increased	Additional description: Gamma-Glutamyltransferase Increased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine Aminotransferase Increased	Additional description: Alanine Aminotransferase Increased		
subjects affected / exposed	4 / 221 (1.81%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases	Additional description: Transaminases		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Aminotransferase Increased	Additional description: Aspartate Aminotransferase Increased		
subjects affected / exposed	3 / 221 (1.36%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Alkaline Phosphatase Increased	Additional description: Blood Alkaline Phosphatase Increased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased	Additional description: Blood Creatinine Increased		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oxygen Saturation Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Oxygen Saturation Decreased		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Fall		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Toxicity To Various Agents subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Toxicity To Various Agents		
	0 / 221 (0.00%)	1 / 111 (0.90%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Femoral Neck Fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Femoral Neck Fracture		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Hip Fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Hip Fracture		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Infusion Related Reaction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Infusion Related Reaction		
	4 / 221 (1.81%)	1 / 111 (0.90%)	
	4 / 4	1 / 1	
	0 / 0	0 / 0	
Cardiac disorders Atrioventricular Block subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Atrioventricular Block		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Pericardial Effusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Pericardial Effusion		
	4 / 221 (1.81%)	0 / 111 (0.00%)	
	0 / 5	0 / 0	
	0 / 1	0 / 0	

Supraventricular Tachycardia subjects affected / exposed	Additional description: Supraventricular Tachycardia		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Acute Coronary Syndrome subjects affected / exposed	Additional description: Acute Coronary Syndrome		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	1 / 1	0 / 0	
	0 / 0	0 / 0	
Sinus Tachycardia subjects affected / exposed	Additional description: Sinus Tachycardia		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Nervous system disorders Dizziness	Additional description: Dizziness		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Cerebral Hypoperfusion subjects affected / exposed	Additional description: Cerebral Hypoperfusion		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Facial Paralysis subjects affected / exposed	Additional description: Facial Paralysis		
	2 / 221 (0.90%)	0 / 111 (0.00%)	
	1 / 2	0 / 0	
	0 / 0	0 / 0	
Ataxia subjects affected / exposed	Additional description: Ataxia		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Syncope subjects affected / exposed	Additional description: Syncope		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Cerebral Haemorrhage	Additional description: Cerebral Haemorrhage		

subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident	Additional description: Cerebrovascular Accident		
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal Cord Compression	Additional description: Spinal Cord Compression		
subjects affected / exposed	0 / 221 (0.00%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 221 (0.90%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia	Additional description: Diplopia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmoplegia	Additional description: Ophthalmoplegia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 221 (0.00%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stomatitis	Additional description: Stomatitis		
	subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
	occurrences causally related to treatment / all	1 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Colitis Microscopic	Additional description: Colitis Microscopic		
	subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
	occurrences causally related to treatment / all	1 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Colitis	Additional description: Colitis		
	subjects affected / exposed	3 / 221 (1.36%)	0 / 111 (0.00%)
	occurrences causally related to treatment / all	3 / 3	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Diarrhoea	Additional description: Diarrhoea		
	subjects affected / exposed	5 / 221 (2.26%)	5 / 111 (4.50%)
	occurrences causally related to treatment / all	5 / 5	3 / 5
	deaths causally related to treatment / all	0 / 0	0 / 0
Ileus	Additional description: Ileus		
	subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Ascites	Additional description: Ascites		
	subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal Obstruction	Additional description: Intestinal Obstruction		
	subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Nausea	Additional description: Nausea		
	subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal Pain	Additional description: Abdominal Pain		

subjects affected / exposed	4 / 221 (1.81%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune Hepatitis	Additional description: Autoimmune Hepatitis		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury	Additional description: Acute Kidney Injury		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis	Additional description: Myositis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain	Additional description: Musculoskeletal Chest Pain		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis	Additional description: Arthritis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain	Additional description: Back Pain		

subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pilonidal Cyst	Additional description: Pilonidal Cyst		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 221 (5.88%)	6 / 111 (5.41%)	
occurrences causally related to treatment / all	0 / 14	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
	Additional description: Lower Respiratory Tract Infection		

subjects affected / exposed	8 / 221 (3.62%)	7 / 111 (6.31%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis	Additional description: Neutropenic Sepsis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
subjects affected / exposed	3 / 221 (1.36%)	3 / 111 (2.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
subjects affected / exposed	0 / 221 (0.00%)	2 / 111 (1.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia	Additional description: Hyperkalaemia		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis	Additional description: Diabetic Ketoacidosis		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Nivolumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	204 / 221 (92.31%)	97 / 111 (87.39%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain	Additional description: Cancer pain		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Basal cell carcinoma	Additional description: Basal cell carcinoma		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Vascular disorders			
Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Peripheral coldness	Additional description: Peripheral coldness		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Brachiocephalic vein thrombosis	Additional description: Brachiocephalic vein thrombosis		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Orthostatic hypotension	Additional description: Orthostatic hypotension		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Embolism	Additional description: Embolism		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hot flush	Additional description: Hot flush		
subjects affected / exposed	9 / 221 (4.07%)	1 / 111 (0.90%)	
occurrences (all)	9	1	
Raynaud's phenomenon	Additional description: Raynaud's phenomenon		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Hypotension	Additional description: Hypotension		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Angiopathy	Additional description: Angiopathy		

subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Superior vena cava occlusion	Additional description: Superior vena cava occlusion		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Ischaemia	Additional description: Ischaemia		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Hypertension	Additional description: Hypertension		
subjects affected / exposed occurrences (all)	5 / 221 (2.26%) 7	4 / 111 (3.60%) 5	
General disorders and administration site conditions			
Catheter site rash	Additional description: Catheter site rash		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed occurrences (all)	11 / 221 (4.98%) 12	2 / 111 (1.80%) 2	
Catheter site hypersensitivity	Additional description: Catheter site hypersensitivity		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed occurrences (all)	11 / 221 (4.98%) 11	4 / 111 (3.60%) 5	
Hyperthermia	Additional description: Hyperthermia		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Swelling	Additional description: Swelling		
subjects affected / exposed occurrences (all)	2 / 221 (0.90%) 3	1 / 111 (0.90%) 1	
Adverse reaction	Additional description: Adverse reaction		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Catheter site erythema	Additional description: Catheter site erythema		

subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Effusion	Additional description: Effusion		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	17 / 221 (7.69%)	8 / 111 (7.21%)	
occurrences (all)	21	11	
Catheter site pruritus	Additional description: Catheter site pruritus		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Adverse drug reaction	Additional description: Adverse drug reaction		
subjects affected / exposed	4 / 221 (1.81%)	0 / 111 (0.00%)	
occurrences (all)	6	0	
Mass	Additional description: Mass		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Chills	Additional description: Chills		
subjects affected / exposed	5 / 221 (2.26%)	0 / 111 (0.00%)	
occurrences (all)	5	0	
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Generalised oedema	Additional description: Generalised oedema		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	4 / 221 (1.81%)	2 / 111 (1.80%)	
occurrences (all)	4	2	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	7 / 221 (3.17%)	4 / 111 (3.60%)	
occurrences (all)	7	4	
Malaise	Additional description: Malaise		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		

subjects affected / exposed	18 / 221 (8.14%)	8 / 111 (7.21%)	
occurrences (all)	18	9	
Facial pain	Additional description: Facial pain		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Catheter site phlebitis	Additional description: Catheter site phlebitis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Cyst	Additional description: Cyst		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Asthenia	Additional description: Asthenia		
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Pain	Additional description: Pain		
subjects affected / exposed	21 / 221 (9.50%)	5 / 111 (4.50%)	
occurrences (all)	22	6	
Feeling cold	Additional description: Feeling cold		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Axillary pain	Additional description: Axillary pain		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Vaccination site pain	Additional description: Vaccination site pain		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Gait disturbance	Additional description: Gait disturbance		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Early satiety	Additional description: Early satiety		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	85 / 221 (38.46%)	33 / 111 (29.73%)	
occurrences (all)	100	35	
General physical health deterioration	Additional description: General physical health deterioration		

subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Infusion site hypoaesthesia	Additional description: Infusion site hypoaesthesia		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Medical device site nodule	Additional description: Medical device site nodule		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Peripheral swelling	Additional description: Peripheral swelling		
subjects affected / exposed occurrences (all)	3 / 221 (1.36%) 3	3 / 111 (2.70%) 4	
Immune system disorders			
Seasonal allergy	Additional description: Seasonal allergy		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 2	0 / 111 (0.00%) 0	
Hypersensitivity	Additional description: Hypersensitivity		
subjects affected / exposed occurrences (all)	2 / 221 (0.90%) 2	1 / 111 (0.90%) 2	
Autoimmune disorder	Additional description: Autoimmune disorder		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Reproductive system and breast disorders			
Genital rash	Additional description: Genital rash		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Penile rash	Additional description: Penile rash		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Breast mass	Additional description: Breast mass		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Nipple pain	Additional description: Nipple pain		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Respiratory, thoracic and mediastinal disorders			

Bronchial obstruction subjects affected / exposed occurrences (all)	Additional description: Bronchial obstruction	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	Additional description: Dyspnoea	
	66 / 221 (29.86%) 74	28 / 111 (25.23%) 32
Dry throat subjects affected / exposed occurrences (all)	Additional description: Dry throat	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Choking subjects affected / exposed occurrences (all)	Additional description: Choking	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Pneumonitis subjects affected / exposed occurrences (all)	Additional description: Pneumonitis	
	2 / 221 (0.90%) 2	0 / 111 (0.00%) 0
Productive cough subjects affected / exposed occurrences (all)	Additional description: Productive cough	
	7 / 221 (3.17%) 7	2 / 111 (1.80%) 2
Wheezing subjects affected / exposed occurrences (all)	Additional description: Wheezing	
	1 / 221 (0.45%) 1	1 / 111 (0.90%) 1
Pleuritic pain subjects affected / exposed occurrences (all)	Additional description: Pleuritic pain	
	3 / 221 (1.36%) 3	1 / 111 (0.90%) 1
Nasal congestion subjects affected / exposed occurrences (all)	Additional description: Nasal congestion	
	1 / 221 (0.45%) 1	1 / 111 (0.90%) 1
Sputum discoloured subjects affected / exposed occurrences (all)	Additional description: Sputum discoloured	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Increased bronchial secretion subjects affected / exposed occurrences (all)	Additional description: Increased bronchial secretion	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Haemoptysis subjects affected / exposed occurrences (all)	Additional description: Haemoptysis	
	2 / 221 (0.90%) 2	2 / 111 (1.80%) 2

Rhinorrhoea	Additional description: Rhinorrhoea	
	1 / 221 (0.45%)	0 / 111 (0.00%)
subjects affected / exposed	1	0
occurrences (all)		
Oropharyngeal pain	Additional description: Oropharyngeal pain	
	6 / 221 (2.71%)	2 / 111 (1.80%)
subjects affected / exposed	6	2
occurrences (all)		
Stridor	Additional description: Stridor	
	0 / 221 (0.00%)	1 / 111 (0.90%)
subjects affected / exposed	0	1
occurrences (all)		
Hypoxia	Additional description: Hypoxia	
	3 / 221 (1.36%)	0 / 111 (0.00%)
subjects affected / exposed	3	0
occurrences (all)		
Pleural effusion	Additional description: Pleural effusion	
	1 / 221 (0.45%)	1 / 111 (0.90%)
subjects affected / exposed	1	2
occurrences (all)		
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease	
	2 / 221 (0.90%)	0 / 111 (0.00%)
subjects affected / exposed	2	0
occurrences (all)		
Cough	Additional description: Cough	
	41 / 221 (18.55%)	21 / 111 (18.92%)
subjects affected / exposed	48	22
occurrences (all)		
Pulmonary embolism	Additional description: Pulmonary embolism	
	2 / 221 (0.90%)	3 / 111 (2.70%)
subjects affected / exposed	2	3
occurrences (all)		
Asthma	Additional description: Asthma	
	1 / 221 (0.45%)	0 / 111 (0.00%)
subjects affected / exposed	1	0
occurrences (all)		
Increased viscosity of bronchial secretion	Additional description: Increased viscosity of bronchial secretion	
	1 / 221 (0.45%)	0 / 111 (0.00%)
subjects affected / exposed	1	0
occurrences (all)		
Epistaxis	Additional description: Epistaxis	
	8 / 221 (3.62%)	1 / 111 (0.90%)
subjects affected / exposed	8	1
occurrences (all)		
Dysphonia	Additional description: Dysphonia	

subjects affected / exposed	5 / 221 (2.26%)	1 / 111 (0.90%)	
occurrences (all)	5	1	
Pneumothorax	Additional description: Pneumothorax		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression	Additional description: Depression		
subjects affected / exposed	6 / 221 (2.71%)	2 / 111 (1.80%)	
occurrences (all)	6	2	
Abnormal dreams	Additional description: Abnormal dreams		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Anxiety	Additional description: Anxiety		
subjects affected / exposed	5 / 221 (2.26%)	1 / 111 (0.90%)	
occurrences (all)	5	1	
Agitation	Additional description: Agitation		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Confusional state	Additional description: Confusional state		
subjects affected / exposed	3 / 221 (1.36%)	1 / 111 (0.90%)	
occurrences (all)	3	1	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	12 / 221 (5.43%)	3 / 111 (2.70%)	
occurrences (all)	12	3	
Depressed mood	Additional description: Depressed mood		
subjects affected / exposed	5 / 221 (2.26%)	2 / 111 (1.80%)	
occurrences (all)	5	2	
Irritability	Additional description: Irritability		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Hallucination	Additional description: Hallucination		
subjects affected / exposed	3 / 221 (1.36%)	1 / 111 (0.90%)	
occurrences (all)	3	1	
Investigations			
Haematocrit decreased	Additional description: Haematocrit decreased		

subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	4 / 221 (1.81%)	1 / 111 (0.90%)	
occurrences (all)	6	1	
Thyroxine decreased	Additional description: Thyroxine decreased		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Tri-iodothyronine free increased	Additional description: Tri-iodothyronine free increased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
White blood cell count increased	Additional description: White blood cell count increased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Blood phosphorus decreased	Additional description: Blood phosphorus decreased		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased	Additional description: C-reactive protein increased		
subjects affected / exposed	2 / 221 (0.90%)	2 / 111 (1.80%)	
occurrences (all)	2	2	
Blood thyroid stimulating hormone decreased	Additional description: Blood thyroid stimulating hormone decreased		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Blood urea increased	Additional description: Blood urea increased		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Creatinine renal clearance decreased	Additional description: Creatinine renal clearance decreased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Amylase increased	Additional description: Amylase increased		
subjects affected / exposed	6 / 221 (2.71%)	1 / 111 (0.90%)	
occurrences (all)	7	2	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	4 / 221 (1.81%)	0 / 111 (0.00%)	
occurrences (all)	6	0	

Tri-iodothyronine increased subjects affected / exposed occurrences (all)	Additional description: Tri-iodothyronine increased	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	Additional description: Aspartate aminotransferase increased	
	7 / 221 (3.17%) 7	0 / 111 (0.00%) 0
Transaminases increased subjects affected / exposed occurrences (all)	Additional description: Transaminases increased	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Tri-iodothyronine decreased subjects affected / exposed occurrences (all)	Additional description: Tri-iodothyronine decreased	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Neutrophil count increased subjects affected / exposed occurrences (all)	Additional description: Neutrophil count increased	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Tri-iodothyronine free decreased subjects affected / exposed occurrences (all)	Additional description: Tri-iodothyronine free decreased	
	2 / 221 (0.90%) 3	0 / 111 (0.00%) 0
Platelet count increased subjects affected / exposed occurrences (all)	Additional description: Platelet count increased	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Blood potassium decreased subjects affected / exposed occurrences (all)	Additional description: Blood potassium decreased	
	1 / 221 (0.45%) 1	1 / 111 (0.90%) 1
Blood calcium decreased subjects affected / exposed occurrences (all)	Additional description: Blood calcium decreased	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Blood testosterone decreased subjects affected / exposed occurrences (all)	Additional description: Blood testosterone decreased	
	0 / 221 (0.00%) 0	2 / 111 (1.80%) 2
Blood phosphorus increased subjects affected / exposed occurrences (all)	Additional description: Blood phosphorus increased	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Blood thyroid stimulating hormone increased	Additional description: Blood thyroid stimulating hormone increased	

subjects affected / exposed	4 / 221 (1.81%)	0 / 111 (0.00%)	
occurrences (all)	6	0	
Thyroxine free increased	Additional description: Thyroxine free increased		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	12 / 221 (5.43%)	9 / 111 (8.11%)	
occurrences (all)	13	9	
Thyroxine free decreased	Additional description: Thyroxine free decreased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased	Additional description: Haemoglobin decreased		
subjects affected / exposed	3 / 221 (1.36%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	9 / 221 (4.07%)	1 / 111 (0.90%)	
occurrences (all)	9	1	
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	8 / 221 (3.62%)	0 / 111 (0.00%)	
occurrences (all)	10	0	
Blood magnesium decreased	Additional description: Blood magnesium decreased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	3 / 221 (1.36%)	2 / 111 (1.80%)	
occurrences (all)	3	4	
Blood creatine phosphokinase	Additional description: Blood creatine phosphokinase		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Protein total decreased	Additional description: Protein total decreased		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	

Lipase increased subjects affected / exposed occurrences (all)	Additional description: Lipase increased		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Injury, poisoning and procedural complications			
	Additional description: Radiation skin injury		
Radiation skin injury subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Arthropod bite subjects affected / exposed occurrences (all)	Additional description: Arthropod bite		
	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Procedural pain subjects affected / exposed occurrences (all)	Additional description: Procedural pain		
	1 / 221 (0.45%) 1	1 / 111 (0.90%) 1	
Contusion subjects affected / exposed occurrences (all)	Additional description: Contusion		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Skin laceration subjects affected / exposed occurrences (all)	Additional description: Skin laceration		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Hand fracture subjects affected / exposed occurrences (all)	Additional description: Hand fracture		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Muscle strain subjects affected / exposed occurrences (all)	Additional description: Muscle strain		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Face injury subjects affected / exposed occurrences (all)	Additional description: Face injury		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Thoracic vertebral fracture subjects affected / exposed occurrences (all)	Additional description: Thoracic vertebral fracture		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Fall subjects affected / exposed occurrences (all)	Additional description: Fall		
	8 / 221 (3.62%) 8	2 / 111 (1.80%) 2	
Road traffic accident	Additional description: Road traffic accident		

subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	14 / 221 (6.33%)	0 / 111 (0.00%)	
occurrences (all)	17	0	
Cardiac disorders			
Sinus tachycardia	Additional description: Sinus tachycardia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Tachycardia	Additional description: Tachycardia		
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Bradycardia	Additional description: Bradycardia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Cardiac dysfunction	Additional description: Cardiac dysfunction		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Pericardial effusion	Additional description: Pericardial effusion		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation	Additional description: Atrial fibrillation		
subjects affected / exposed	1 / 221 (0.45%)	2 / 111 (1.80%)	
occurrences (all)	1	2	
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Peripheral motor neuropathy	Additional description: Peripheral motor neuropathy		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Syncope	Additional description: Syncope		

subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	3 / 221 (1.36%)	1 / 111 (0.90%)	
occurrences (all)	3	1	
Drooling	Additional description: Drooling		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Lethargy	Additional description: Lethargy		
subjects affected / exposed	12 / 221 (5.43%)	6 / 111 (5.41%)	
occurrences (all)	14	6	
Headache	Additional description: Headache		
subjects affected / exposed	13 / 221 (5.88%)	4 / 111 (3.60%)	
occurrences (all)	20	5	
Burning sensation	Additional description: Burning sensation		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Dizziness postural	Additional description: Dizziness postural		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Taste disorder	Additional description: Taste disorder		
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Neuralgia	Additional description: Neuralgia		
subjects affected / exposed	2 / 221 (0.90%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Peroneal nerve palsy	Additional description: Peroneal nerve palsy		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Seizure	Additional description: Seizure		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia	Additional description: Hypoaesthesia		

subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	11 / 221 (4.98%)	2 / 111 (1.80%)	
occurrences (all)	11	2	
Balance disorder	Additional description: Balance disorder		
subjects affected / exposed	4 / 221 (1.81%)	0 / 111 (0.00%)	
occurrences (all)	4	0	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	6 / 221 (2.71%)	1 / 111 (0.90%)	
occurrences (all)	6	1	
Anosmia	Additional description: Anosmia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Migraine	Additional description: Migraine		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Trigeminal neuralgia	Additional description: Trigeminal neuralgia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Somnolence	Additional description: Somnolence		
subjects affected / exposed	4 / 221 (1.81%)	0 / 111 (0.00%)	
occurrences (all)	4	0	
Tremor	Additional description: Tremor		
subjects affected / exposed	3 / 221 (1.36%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Hypersomnia	Additional description: Hypersomnia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	1 / 221 (0.45%)	2 / 111 (1.80%)	
occurrences (all)	1	2	
Spinal cord compression	Additional description: Spinal cord compression		
subjects affected / exposed	2 / 221 (0.90%)	1 / 111 (0.90%)	
occurrences (all)	2	1	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		

subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Lymphadenopathy	Additional description: Lymphadenopathy		
subjects affected / exposed occurrences (all)	2 / 221 (0.90%) 2	0 / 111 (0.00%) 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Anaemia	Additional description: Anaemia		
subjects affected / exposed occurrences (all)	22 / 221 (9.95%) 29	4 / 111 (3.60%) 5	
Ear and labyrinth disorders			
Vertigo	Additional description: Vertigo		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Hypoacusis	Additional description: Hypoacusis		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Ear pain	Additional description: Ear pain		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	2 / 111 (1.80%) 2	
Cerumen impaction	Additional description: Cerumen impaction		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Eye disorders			
Glare	Additional description: Glare		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Dry eye	Additional description: Dry eye		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	3 / 111 (2.70%) 3	
Lacrimation increased	Additional description: Lacrimation increased		

subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Vision blurred	Additional description: Vision blurred		
subjects affected / exposed	4 / 221 (1.81%)	2 / 111 (1.80%)	
occurrences (all)	4	2	
Macular oedema	Additional description: Macular oedema		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	2	
Blepharitis	Additional description: Blepharitis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Eye swelling	Additional description: Eye swelling		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Eye pruritus	Additional description: Eye pruritus		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Visual impairment	Additional description: Visual impairment		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Eye pain	Additional description: Eye pain		
subjects affected / exposed	3 / 221 (1.36%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Photopsia	Additional description: Photopsia		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Cystoid macular oedema	Additional description: Cystoid macular oedema		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Eye irritation	Additional description: Eye irritation		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Foreign body sensation in eyes	Additional description: Foreign body sensation in eyes		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Uveitis	Additional description: Uveitis		

subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Gastrointestinal disorders			
Constipation	Additional description: Constipation		
subjects affected / exposed occurrences (all)	60 / 221 (27.15%) 69	27 / 111 (24.32%) 29	
Paraesthesia oral	Additional description: Paraesthesia oral		
subjects affected / exposed occurrences (all)	2 / 221 (0.90%) 2	0 / 111 (0.00%) 0	
Hiatus hernia	Additional description: Hiatus hernia		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Abdominal mass	Additional description: Abdominal mass		
subjects affected / exposed occurrences (all)	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Abdominal pain lower	Additional description: Abdominal pain lower		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	1 / 111 (0.90%) 1	
Glossodynia	Additional description: Glossodynia		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Toothache	Additional description: Toothache		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Anal incontinence	Additional description: Anal incontinence		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Nausea	Additional description: Nausea		
subjects affected / exposed occurrences (all)	47 / 221 (21.27%) 66	23 / 111 (20.72%) 24	
Frequent bowel movements	Additional description: Frequent bowel movements		
subjects affected / exposed occurrences (all)	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed occurrences (all)	6 / 221 (2.71%) 6	6 / 111 (5.41%) 7	

Tongue ulceration subjects affected / exposed occurrences (all)	Additional description: Tongue ulceration	
	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1
Rectal haemorrhage subjects affected / exposed occurrences (all)	Additional description: Rectal haemorrhage	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Proctalgia subjects affected / exposed occurrences (all)	Additional description: Proctalgia	
	1 / 221 (0.45%) 1	1 / 111 (0.90%) 1
Diarrhoea subjects affected / exposed occurrences (all)	Additional description: Diarrhoea	
	41 / 221 (18.55%) 66	17 / 111 (15.32%) 29
Haemorrhoids subjects affected / exposed occurrences (all)	Additional description: Haemorrhoids	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Mouth ulceration subjects affected / exposed occurrences (all)	Additional description: Mouth ulceration	
	2 / 221 (0.90%) 2	1 / 111 (0.90%) 1
Dry mouth subjects affected / exposed occurrences (all)	Additional description: Dry mouth	
	8 / 221 (3.62%) 8	8 / 111 (7.21%) 8
Oral pain subjects affected / exposed occurrences (all)	Additional description: Oral pain	
	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1
Stomatitis subjects affected / exposed occurrences (all)	Additional description: Stomatitis	
	8 / 221 (3.62%) 9	1 / 111 (0.90%) 1
Flatulence subjects affected / exposed occurrences (all)	Additional description: Flatulence	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	Additional description: Gastrooesophageal reflux disease	
	6 / 221 (2.71%) 6	0 / 111 (0.00%) 0
Abdominal discomfort subjects affected / exposed occurrences (all)	Additional description: Abdominal discomfort	
	5 / 221 (2.26%) 5	1 / 111 (0.90%) 1

Dysphagia	Additional description: Dysphagia	
subjects affected / exposed	3 / 221 (1.36%)	3 / 111 (2.70%)
occurrences (all)	3	3
Tongue haemorrhage	Additional description: Tongue haemorrhage	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Dyspepsia	Additional description: Dyspepsia	
subjects affected / exposed	6 / 221 (2.71%)	4 / 111 (3.60%)
occurrences (all)	6	4
Haematemesis	Additional description: Haematemesis	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Lip dry	Additional description: Lip dry	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Colitis	Additional description: Colitis	
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)
occurrences (all)	1	2
Pancreatitis	Additional description: Pancreatitis	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Abdominal pain upper	Additional description: Abdominal pain upper	
subjects affected / exposed	4 / 221 (1.81%)	2 / 111 (1.80%)
occurrences (all)	4	2
Hyperaesthesia teeth	Additional description: Hyperaesthesia teeth	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Gingival pain	Additional description: Gingival pain	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Melaena	Additional description: Melaena	
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)
occurrences (all)	1	1
Swollen tongue	Additional description: Swollen tongue	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0

Ascites subjects affected / exposed occurrences (all)	Additional description: Ascites		
	6 / 221 (2.71%)	2 / 111 (1.80%)	
	8	2	
Abdominal distension subjects affected / exposed occurrences (all)	Additional description: Abdominal distension		
	5 / 221 (2.26%)	4 / 111 (3.60%)	
	6	5	
Vomiting subjects affected / exposed occurrences (all)	Additional description: Vomiting		
	25 / 221 (11.31%)	9 / 111 (8.11%)	
	28	10	
Hepatobiliary disorders			
Hepatotoxicity subjects affected / exposed occurrences (all)	Additional description: Hepatotoxicity		
	2 / 221 (0.90%)	0 / 111 (0.00%)	
	2	0	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	Additional description: Alopecia		
	4 / 221 (1.81%)	0 / 111 (0.00%)	
	4	0	
Rash subjects affected / exposed occurrences (all)	Additional description: Rash		
	27 / 221 (12.22%)	4 / 111 (3.60%)	
	35	5	
Rash erythematous subjects affected / exposed occurrences (all)	Additional description: Rash erythematous		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	1	0	
Dry skin subjects affected / exposed occurrences (all)	Additional description: Dry skin		
	11 / 221 (4.98%)	4 / 111 (3.60%)	
	11	4	
Lichen planus subjects affected / exposed occurrences (all)	Additional description: Lichen planus		
	1 / 221 (0.45%)	0 / 111 (0.00%)	
	1	0	
Erythema subjects affected / exposed occurrences (all)	Additional description: Erythema		
	3 / 221 (1.36%)	0 / 111 (0.00%)	
	4	0	
Urticaria subjects affected / exposed occurrences (all)	Additional description: Urticaria		
	1 / 221 (0.45%)	1 / 111 (0.90%)	
	1	1	
Night sweats	Additional description: Night sweats		

subjects affected / exposed	7 / 221 (3.17%)	4 / 111 (3.60%)	
occurrences (all)	7	4	
Decubitus ulcer	Additional description: Decubitus ulcer		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Rash pruritic	Additional description: Rash pruritic		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Psoriasis	Additional description: Psoriasis		
subjects affected / exposed	3 / 221 (1.36%)	0 / 111 (0.00%)	
occurrences (all)	3	0	
Rash maculo-papular	Additional description: Rash maculo-papular		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Skin disorder	Additional description: Skin disorder		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction	Additional description: Photosensitivity reaction		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis	Additional description: Hyperhidrosis		
subjects affected / exposed	3 / 221 (1.36%)	3 / 111 (2.70%)	
occurrences (all)	3	3	
Pain of skin	Additional description: Pain of skin		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Pruritus	Additional description: Pruritus		
subjects affected / exposed	28 / 221 (12.67%)	11 / 111 (9.91%)	
occurrences (all)	31	14	
Renal and urinary disorders			
Haematuria	Additional description: Haematuria		
subjects affected / exposed	2 / 221 (0.90%)	1 / 111 (0.90%)	
occurrences (all)	2	3	
Urinary incontinence	Additional description: Urinary incontinence		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	

Urinary retention subjects affected / exposed occurrences (all)	Additional description: Urinary retention		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Dysuria subjects affected / exposed occurrences (all)	Additional description: Dysuria		
	3 / 221 (1.36%) 3	0 / 111 (0.00%) 0	
Chromaturia subjects affected / exposed occurrences (all)	Additional description: Chromaturia		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Nocturia subjects affected / exposed occurrences (all)	Additional description: Nocturia		
	2 / 221 (0.90%) 3	0 / 111 (0.00%) 0	
Proteinuria subjects affected / exposed occurrences (all)	Additional description: Proteinuria		
	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Renal vein thrombosis subjects affected / exposed occurrences (all)	Additional description: Renal vein thrombosis		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Pollakiuria subjects affected / exposed occurrences (all)	Additional description: Pollakiuria		
	0 / 221 (0.00%) 0	1 / 111 (0.90%) 1	
Renal impairment subjects affected / exposed occurrences (all)	Additional description: Renal impairment		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	
Acute kidney injury subjects affected / exposed occurrences (all)	Additional description: Acute kidney injury		
	2 / 221 (0.90%) 2	0 / 111 (0.00%) 0	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)			
	Additional description: Hypothyroidism		
	12 / 221 (5.43%) 12	1 / 111 (0.90%) 1	
Hyperthyroidism subjects affected / exposed occurrences (all)	Additional description: Hyperthyroidism		
	3 / 221 (1.36%) 3	0 / 111 (0.00%) 0	
Musculoskeletal and connective tissue disorders			

Flank pain	Additional description: Flank pain	
subjects affected / exposed	3 / 221 (1.36%)	3 / 111 (2.70%)
occurrences (all)	3	3
Pain in jaw	Additional description: Pain in jaw	
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	1
Musculoskeletal stiffness	Additional description: Musculoskeletal stiffness	
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)
occurrences (all)	0	1
Musculoskeletal chest pain	Additional description: Musculoskeletal chest pain	
subjects affected / exposed	12 / 221 (5.43%)	2 / 111 (1.80%)
occurrences (all)	14	3
Musculoskeletal pain	Additional description: Musculoskeletal pain	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Myalgia	Additional description: Myalgia	
subjects affected / exposed	9 / 221 (4.07%)	2 / 111 (1.80%)
occurrences (all)	9	2
Inguinal mass	Additional description: Inguinal mass	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Neck pain	Additional description: Neck pain	
subjects affected / exposed	4 / 221 (1.81%)	1 / 111 (0.90%)
occurrences (all)	4	1
Limb discomfort	Additional description: Limb discomfort	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Pain in extremity	Additional description: Pain in extremity	
subjects affected / exposed	5 / 221 (2.26%)	1 / 111 (0.90%)
occurrences (all)	5	1
Chest wall mass	Additional description: Chest wall mass	
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences (all)	1	0
Joint stiffness	Additional description: Joint stiffness	
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)
occurrences (all)	1	1

Muscle spasms subjects affected / exposed occurrences (all)	Additional description: Muscle spasms	
	3 / 221 (1.36%) 3	3 / 111 (2.70%) 3
Arthralgia subjects affected / exposed occurrences (all)	Additional description: Arthralgia	
	31 / 221 (14.03%) 38	18 / 111 (16.22%) 21
Arthritis subjects affected / exposed occurrences (all)	Additional description: Arthritis	
	2 / 221 (0.90%) 2	1 / 111 (0.90%) 1
Muscular weakness subjects affected / exposed occurrences (all)	Additional description: Muscular weakness	
	5 / 221 (2.26%) 5	1 / 111 (0.90%) 1
Tendonitis subjects affected / exposed occurrences (all)	Additional description: Tendonitis	
	1 / 221 (0.45%) 1	1 / 111 (0.90%) 1
Arthropathy subjects affected / exposed occurrences (all)	Additional description: Arthropathy	
	1 / 221 (0.45%) 2	0 / 111 (0.00%) 0
Joint swelling subjects affected / exposed occurrences (all)	Additional description: Joint swelling	
	3 / 221 (1.36%) 3	1 / 111 (0.90%) 1
Groin pain subjects affected / exposed occurrences (all)	Additional description: Groin pain	
	2 / 221 (0.90%) 2	0 / 111 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	Additional description: Back pain	
	16 / 221 (7.24%) 16	9 / 111 (8.11%) 10
Infections and infestations		
Skin infection subjects affected / exposed occurrences (all)	Additional description: Skin infection	
	2 / 221 (0.90%) 2	0 / 111 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	Additional description: COVID-19	
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0
Tooth infection	Additional description: Tooth infection	

subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Oral candidiasis	Additional description: Oral candidiasis		
subjects affected / exposed	10 / 221 (4.52%)	7 / 111 (6.31%)	
occurrences (all)	10	8	
Staphylococcal infection	Additional description: Staphylococcal infection		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Gastroenteritis viral	Additional description: Gastroenteritis viral		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Spontaneous bacterial peritonitis	Additional description: Spontaneous bacterial peritonitis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis	Additional description: Conjunctivitis		
subjects affected / exposed	3 / 221 (1.36%)	2 / 111 (1.80%)	
occurrences (all)	5	2	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	1 / 221 (0.45%)	1 / 111 (0.90%)	
occurrences (all)	1	1	
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	4 / 221 (1.81%)	2 / 111 (1.80%)	
occurrences (all)	4	2	
Wound infection	Additional description: Wound infection		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	2	0	
Laryngitis	Additional description: Laryngitis		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Infection	Additional description: Infection		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Influenza	Additional description: Influenza		

subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	

Viral infection	Additional description: Viral infection		
subjects affected / exposed	2 / 221 (0.90%)	2 / 111 (1.80%)	
occurrences (all)	2	2	

Candida infection	Additional description: Candida infection		
subjects affected / exposed	6 / 221 (2.71%)	1 / 111 (0.90%)	
occurrences (all)	6	1	

Rash pustular	Additional description: Rash pustular		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	

Ear infection	Additional description: Ear infection		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	

Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	37 / 221 (16.74%)	12 / 111 (10.81%)	
occurrences (all)	45	14	

Lymphangitis	Additional description: Lymphangitis		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	

Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	

Mucosal infection	Additional description: Mucosal infection		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	

Cystitis	Additional description: Cystitis		
subjects affected / exposed	2 / 221 (0.90%)	0 / 111 (0.00%)	
occurrences (all)	2	0	

Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	7 / 221 (3.17%)	5 / 111 (4.50%)	
occurrences (all)	7	5	

Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	8 / 221 (3.62%)	5 / 111 (4.50%)	
occurrences (all)	8	5	

Urinary tract infection	Additional description: Urinary tract infection		

subjects affected / exposed	10 / 221 (4.52%)	4 / 111 (3.60%)	
occurrences (all)	14	5	
Vulvovaginal candidiasis	Additional description: Vulvovaginal candidiasis		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Eye infection	Additional description: Eye infection		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Gingivitis	Additional description: Gingivitis		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Oral herpes	Additional description: Oral herpes		
subjects affected / exposed	4 / 221 (1.81%)	1 / 111 (0.90%)	
occurrences (all)	4	1	
Paronychia	Additional description: Paronychia		
subjects affected / exposed	0 / 221 (0.00%)	1 / 111 (0.90%)	
occurrences (all)	0	1	
Tinea pedis	Additional description: Tinea pedis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Medical device site infection	Additional description: Medical device site infection		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Oesophageal candidiasis	Additional description: Oesophageal candidiasis		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypophosphataemia	Additional description: Hypophosphataemia		
subjects affected / exposed	0 / 221 (0.00%)	2 / 111 (1.80%)	
occurrences (all)	0	2	
Hypophagia	Additional description: Hypophagia		
subjects affected / exposed	1 / 221 (0.45%)	0 / 111 (0.00%)	
occurrences (all)	1	0	

Decreased appetite subjects affected / exposed occurrences (all)	Additional description: Decreased appetite	
	44 / 221 (19.91%)	26 / 111 (23.42%)
	45	29
Hyperglycaemia subjects affected / exposed occurrences (all)	Additional description: Hyperglycaemia	
	1 / 221 (0.45%)	0 / 111 (0.00%)
	1	0
Dehydration subjects affected / exposed occurrences (all)	Additional description: Dehydration	
	3 / 221 (1.36%)	2 / 111 (1.80%)
	3	2
Hypoalbuminaemia subjects affected / exposed occurrences (all)	Additional description: Hypoalbuminaemia	
	3 / 221 (1.36%)	0 / 111 (0.00%)
	3	0
Hypoglycaemia subjects affected / exposed occurrences (all)	Additional description: Hypoglycaemia	
	1 / 221 (0.45%)	0 / 111 (0.00%)
	1	0
Polydipsia subjects affected / exposed occurrences (all)	Additional description: Polydipsia	
	0 / 221 (0.00%)	1 / 111 (0.90%)
	0	1
Vitamin D deficiency subjects affected / exposed occurrences (all)	Additional description: Vitamin D deficiency	
	1 / 221 (0.45%)	0 / 111 (0.00%)
	1	0
Hyponatraemia subjects affected / exposed occurrences (all)	Additional description: Hyponatraemia	
	2 / 221 (0.90%)	2 / 111 (1.80%)
	3	2
Hypokalaemia subjects affected / exposed occurrences (all)	Additional description: Hypokalaemia	
	1 / 221 (0.45%)	0 / 111 (0.00%)
	1	0
Gout subjects affected / exposed occurrences (all)	Additional description: Gout	
	1 / 221 (0.45%)	0 / 111 (0.00%)
	1	0
Hyperamylasaemia subjects affected / exposed occurrences (all)	Additional description: Hyperamylasaemia	
	1 / 221 (0.45%)	0 / 111 (0.00%)
	1	0
Hypercalcaemia subjects affected / exposed occurrences (all)	Additional description: Hypercalcaemia	
	0 / 221 (0.00%)	1 / 111 (0.90%)
	0	2

Hyperkalaemia subjects affected / exposed occurrences (all)	Additional description: Hyperkalaemia		
	3 / 221 (1.36%) 4	0 / 111 (0.00%) 0	
Hypomagnesaemia subjects affected / exposed occurrences (all)	Additional description: Hypomagnesaemia		
	1 / 221 (0.45%) 1	0 / 111 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2018	V3 - Assessment and treatment windows defined; screening and baseline factors differentiated
26 April 2018	V4 - AEs to be reported from start of treatment rather than consent
14 February 2019	V6 - addition of progression free survival as co-primary endpoint; inclusion of second line treatment in eligibility criteria.
11 June 2020	V7 - Addition of +/-3 days for CT scans; nivolumab administration updated to align with new IB; clarification of how co-primary endpoints were to be analysed; removal of interim analyses
13 November 2020	V8 - updated translational objectives, endpoints and analysis section; updated modified RECIST link

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

COVID-19 pandemic led to early termination of recruitment; however, the study was four participants short of target, and, given the sample size was based on number of events rather than number of people, the study could achieve the intended power.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34656227>