



Clinical trial results:

A Phase II Single-arm, Open-label Monotherapy Clinical Trial of Pembrolizumab (MK-3475) in Locally Advanced/Metastatic Renal Cell Carcinoma (mRCC) (KEYNOTE-427) Summary

EudraCT number	2016-000589-47
Trial protocol	DE DK GB ES CZ PL
Global end of trial date	01 April 2022

Results information

Result version number	v1 (current)
This version publication date	06 April 2023
First version publication date	06 April 2023

Trial information

Trial identification

Sponsor protocol code	3475-427
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02853344
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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	01 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 February 2021
Global end of trial reached?	Yes
Global end of trial date	01 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the safety and efficacy of monotherapy pembrolizumab (MK-3475) in participants with renal cell carcinoma (RCC). There will be two cohorts in this study: Cohort A will consist of participants with clear cell (cc) RCC and Cohort B will consist of participants with non-clear cell (ncc) RCC.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	63 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	United States: 59
Worldwide total number of subjects	275
EEA total number of subjects	111

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)	164
From 65 to 84 years	107
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who met the following key criteria at screening were eligible for enrollment:

1. Histologically confirmed diagnosis of ccRCC or nccRCC.
2. Had locally advanced/metastatic disease.
3. Had measurable disease per RECIST 1.1 as assessed by BICR.
4. Had received no prior systemic therapy for advanced RCC.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: Clear Cell RCC

Arm description:

Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months).

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 Keytruda
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg intravenously (IV) every 3 weeks (Q3W)

Arm title	Cohort B: Non-clear Cell RCC
------------------	------------------------------

Arm description:

Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months).

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 Keytruda
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg intravenously (IV) every 3 weeks (Q3W)

Number of subjects in period 1	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC
Started	110	165
Received Second Course of Pembrolizumab	3	5
Completed	0	0
Not completed	110	165
Consent withdrawn by subject	2	4
Death	70	112
Participation in Study Terminated by Sponsor	37	48
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort A: Clear Cell RCC
Reporting group description:	
Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months).	
Reporting group title	Cohort B: Non-clear Cell RCC
Reporting group description:	
Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months).	

Reporting group values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC	Total
Number of subjects	110	165	275
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)	58	106	164
From 65-84 years	49	58	107
85 years and over	3	1	4
Age Continuous			
Units: Years			
arithmetic mean	62.9	60.0	
standard deviation	± 11.0	± 12.3	-
Sex: Female, Male			
Units: Participants			
Female	24	56	80
Male	86	109	195
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	11	17	28
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	98	145	243
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	104	156	260
Unknown or Not Reported	4	8	12

End points

End points reporting groups

Reporting group title	Cohort A: Clear Cell RCC
Reporting group description: Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months).	
Reporting group title	Cohort B: Non-clear Cell RCC
Reporting group description: Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months).	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR) ^[1]
End point description: ORR was defined as the percentage of participants who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) as assessed by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The population analyzed included all allocated participants who received at least one dose of study treatment.	
End point type	Primary
End point timeframe: Up to approximately 66 months	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analyses were planned for this endpoint.	

End point values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	165		
Units: Percentage of Participants				
number (confidence interval 95%)	36.4 (27.4 to 46.1)	26.7 (20.1 to 34.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
End point description: For participants who demonstrated a confirmed Complete Response (CR: disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, DOR was defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumor assessment. Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions as well as an absolute increase of at least 5 mm in the sum of diameters. The appearance of one or more new lesions was also considered PD.	

DOR assessments were based on BICR. The DOR as assessed using RECIST 1.1 for all participants who experienced a confirmed CR or PR is presented. The population analyzed included all allocated participants who received at least one dose of study treatment and had confirmed CR or PR.

End point type	Secondary
End point timeframe:	
Up to approximately 66 months	

End point values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110 ^[2]	165 ^[3]		
Units: Months				
median (confidence interval 95%)	18.9 (2.3 to 9999)	29.0 (2.8 to 9999)		

Notes:

[2] - 9999 = upper limit not reached due to insufficient number of responding participants with PD.

[3] - 9999 = upper limit not reached due to insufficient number of responding participants with PD.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
End point description:	
DCR is defined as the percentage of participants who have achieved CR, PR, or Stable Disease (SD) for at least 6 months based on assessments by the BICR per RECIST 1.1. CR is defined as disappearance of all target lesions, PR is defined as at least a 30% decrease in the sum of diameters of target lesions, SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered PD. The population analyzed included all allocated participants who received at least one dose of study treatment.	
End point type	Secondary
End point timeframe:	
Up to approximately 66 months	

End point values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	165		
Units: Percentage of Participants				
number (confidence interval 95%)	58.2 (48.4 to 67.5)	43.0 (35.4 to 51.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
End point description: PFS is defined as the time from first dose of study treatment to the first documented progressive disease (PD) per RECIST 1.1 based on BICR, or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is defined as $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. The appearance of one or more new lesions is also considered PD. The population analyzed included all allocated participants who received at least one dose of study treatment.	
End point type	Secondary
End point timeframe: Up to approximately 66 months	

End point values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	165		
Units: Months				
median (confidence interval 95%)	7.1 (5.6 to 11.0)	4.2 (2.9 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description: OS was defined as the time from first dose of study treatment to death due to any cause. The population analyzed included all allocated participants who received at least one dose of study treatment.	
End point type	Secondary
End point timeframe: Up to approximately 66 months	

End point values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	165		
Units: Months				
median (confidence interval 95%)	40.7 (31.1 to 52.6)	29.9 (24.3 to 37.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced an Adverse Event (AE)

End point title	Number of Participants Who Experienced an Adverse Event (AE)
-----------------	--

End point description:

An adverse event is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. The population analyzed included all allocated participants who received at least one dose of study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to approximately 27 months

End point values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	165		
Units: Participants	109	155		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Drug Due to an AE

End point title	Number of Participants Who Discontinued Study Drug Due to an AE
-----------------	---

End point description:

An adverse event is defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. The population analyzed included all allocated participants who received at least one dose of study treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to approximately 24 months

End point values	Cohort A: Clear Cell RCC	Cohort B: Non-clear Cell RCC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	165		
Units: Participants	23	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 66 months

Adverse event reporting additional description:

Safety analysis population includes all participants who received at least one dose of study treatment. Progression of cancer under study was not an AE unless considered related to study treatment. Therefore, MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" unrelated to the drug are excluded.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.1
--------------------	------

Reporting groups

Reporting group title	Cohort B: nccRCC First Course
-----------------------	-------------------------------

Reporting group description:

Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months)

Reporting group title	Cohort B: nccRCC Second Course
-----------------------	--------------------------------

Reporting group description:

Participants with non-clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months). Eligible participants with nccRCC who experienced disease progression received up to 17 additional doses of pembrolizumab.

Reporting group title	Cohort A: ccRCC First Course
-----------------------	------------------------------

Reporting group description:

Participants with clear cell RCC received pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W) for up to 35 doses (approximately 24 months).

Reporting group title	Cohort A: ccRCC Second Course
-----------------------	-------------------------------

Reporting group description:

Participants with clear cell RCC received pembrolizumab 200 mg IV Q3W for up to 35 doses (approximately 24 months). Eligible participants with ccRCC who experienced disease progression received up to 17 additional doses of pembrolizumab.

Serious adverse events	Cohort B: nccRCC First Course	Cohort B: nccRCC Second Course	Cohort A: ccRCC First Course
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 165 (28.48%)	0 / 5 (0.00%)	52 / 110 (47.27%)
number of deaths (all causes)	113	0	71
number of deaths resulting from adverse events	2	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell small lymphocytic lymphoma			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			

subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery aneurysm			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Hypotension			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Chest pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Asthenia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Stent-graft endoleak			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 165 (1.82%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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			
Anxiety			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Delirium			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Product issues			
Device dislocation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Joint dislocation			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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 compression fracture			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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 failure			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Atrial thrombosis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Left ventricular failure			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Myocarditis			
subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	0 / 110 (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
Pericardial effusion			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Bell's palsy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemorrhage intracranial			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Encephalopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Myasthenic syndrome			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuritis			

subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Myelopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
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 cord compression			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Lymphadenopathy			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	3 / 165 (1.82%)	0 / 5 (0.00%)	4 / 110 (3.64%)
occurrences causally related to treatment / all	3 / 3	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	4 / 110 (3.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Pancreatitis acute			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			

subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Hepatitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Hepatitis cholestatic			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			

subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
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			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Myositis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Pathological fracture			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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

Polyarthritis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Bronchitis			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (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
Urosepsis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adult failure to thrive			

subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	2 / 110 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 165 (0.00%)	0 / 5 (0.00%)	3 / 110 (2.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort A: ccRCC Second Course		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell small lymphocytic lymphoma			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral artery aneurysm			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral artery stenosis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stent-graft endoleak			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device dislocation			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac failure			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial thrombosis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bell's palsy			

subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myasthenic syndrome				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuritis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myelopathy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal pain upper				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis cholestatic			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Nephritis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myositis			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Polyarthritis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular device infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			

subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Adult failure to thrive				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Type 2 diabetes mellitus				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Type 1 diabetes mellitus				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypophosphataemia				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 3 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				

subjects affected / exposed	0 / 3 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort B: nccRCC First Course	Cohort B: nccRCC Second Course	Cohort A: ccRCC First Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	142 / 165 (86.06%)	3 / 5 (60.00%)	105 / 110 (95.45%)
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 165 (6.67%)	0 / 5 (0.00%)	9 / 110 (8.18%)
occurrences (all)	12	0	11
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 165 (11.52%)	1 / 5 (20.00%)	13 / 110 (11.82%)
occurrences (all)	22	1	23
Catheter site pain			
subjects affected / exposed	2 / 165 (1.21%)	0 / 5 (0.00%)	0 / 110 (0.00%)
occurrences (all)	2	0	0
Chest pain			
subjects affected / exposed	9 / 165 (5.45%)	0 / 5 (0.00%)	7 / 110 (6.36%)
occurrences (all)	10	0	7
Fatigue			
subjects affected / exposed	42 / 165 (25.45%)	0 / 5 (0.00%)	43 / 110 (39.09%)
occurrences (all)	48	0	51
Influenza like illness			
subjects affected / exposed	7 / 165 (4.24%)	0 / 5 (0.00%)	10 / 110 (9.09%)
occurrences (all)	13	0	24
Oedema peripheral			
subjects affected / exposed	14 / 165 (8.48%)	0 / 5 (0.00%)	8 / 110 (7.27%)
occurrences (all)	16	0	9
Pyrexia			
subjects affected / exposed	17 / 165 (10.30%)	1 / 5 (20.00%)	8 / 110 (7.27%)
occurrences (all)	21	1	8

Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 165 (0.00%) 0	0 / 5 (0.00%) 0	0 / 110 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	26 / 165 (15.76%) 30	0 / 5 (0.00%) 0	25 / 110 (22.73%) 30
Dyspnoea subjects affected / exposed occurrences (all)	15 / 165 (9.09%) 19	0 / 5 (0.00%) 0	16 / 110 (14.55%) 19
Productive cough subjects affected / exposed occurrences (all)	9 / 165 (5.45%) 11	0 / 5 (0.00%) 0	2 / 110 (1.82%) 2
Wheezing subjects affected / exposed occurrences (all)	1 / 165 (0.61%) 1	0 / 5 (0.00%) 0	2 / 110 (1.82%) 2
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	6 / 165 (3.64%) 7	0 / 5 (0.00%) 0	8 / 110 (7.27%) 8
Insomnia subjects affected / exposed occurrences (all)	13 / 165 (7.88%) 14	0 / 5 (0.00%) 0	10 / 110 (9.09%) 13
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	15 / 165 (9.09%) 17	0 / 5 (0.00%) 0	15 / 110 (13.64%) 15
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	12 / 165 (7.27%) 13	0 / 5 (0.00%) 0	12 / 110 (10.91%) 15
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	13 / 165 (7.88%) 15	0 / 5 (0.00%) 0	8 / 110 (7.27%) 8
Weight decreased			

subjects affected / exposed occurrences (all)	10 / 165 (6.06%) 10	0 / 5 (0.00%) 0	4 / 110 (3.64%) 4
Neutrophil count decreased subjects affected / exposed occurrences (all)	3 / 165 (1.82%) 9	0 / 5 (0.00%) 0	1 / 110 (0.91%) 1
Lymphocyte count decreased subjects affected / exposed occurrences (all)	5 / 165 (3.03%) 11	0 / 5 (0.00%) 0	7 / 110 (6.36%) 9
Blood creatinine increased subjects affected / exposed occurrences (all)	12 / 165 (7.27%) 15	0 / 5 (0.00%) 0	19 / 110 (17.27%) 23
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	1 / 165 (0.61%) 1	1 / 5 (20.00%) 1	1 / 110 (0.91%) 2
Nervous system disorders Headache subjects affected / exposed occurrences (all)	18 / 165 (10.91%) 24	0 / 5 (0.00%) 0	13 / 110 (11.82%) 17
Dizziness subjects affected / exposed occurrences (all)	6 / 165 (3.64%) 9	0 / 5 (0.00%) 0	10 / 110 (9.09%) 13
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	19 / 165 (11.52%) 24	0 / 5 (0.00%) 0	15 / 110 (13.64%) 16
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	18 / 165 (10.91%) 23	0 / 5 (0.00%) 0	23 / 110 (20.91%) 23
Abdominal pain subjects affected / exposed occurrences (all)	22 / 165 (13.33%) 28	0 / 5 (0.00%) 0	10 / 110 (9.09%) 11
Vomiting subjects affected / exposed occurrences (all)	27 / 165 (16.36%) 37	0 / 5 (0.00%) 0	8 / 110 (7.27%) 9
Nausea			

subjects affected / exposed occurrences (all)	28 / 165 (16.97%) 38	0 / 5 (0.00%) 0	22 / 110 (20.00%) 26
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 165 (0.61%) 1	1 / 5 (20.00%) 1	0 / 110 (0.00%) 0
Dyspepsia subjects affected / exposed occurrences (all)	6 / 165 (3.64%) 6	0 / 5 (0.00%) 0	8 / 110 (7.27%) 8
Dry mouth subjects affected / exposed occurrences (all)	15 / 165 (9.09%) 18	0 / 5 (0.00%) 0	13 / 110 (11.82%) 16
Diarrhoea subjects affected / exposed occurrences (all)	40 / 165 (24.24%) 65	0 / 5 (0.00%) 0	35 / 110 (31.82%) 58
Skin and subcutaneous tissue disorders			
Rash maculo-papular subjects affected / exposed occurrences (all)	10 / 165 (6.06%) 11	0 / 5 (0.00%) 0	8 / 110 (7.27%) 8
Dry skin subjects affected / exposed occurrences (all)	10 / 165 (6.06%) 11	0 / 5 (0.00%) 0	7 / 110 (6.36%) 9
Pruritus subjects affected / exposed occurrences (all)	37 / 165 (22.42%) 48	1 / 5 (20.00%) 1	41 / 110 (37.27%) 54
Rash subjects affected / exposed occurrences (all)	19 / 165 (11.52%) 24	0 / 5 (0.00%) 0	17 / 110 (15.45%) 23
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	6 / 165 (3.64%) 9	0 / 5 (0.00%) 0	6 / 110 (5.45%) 6
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	26 / 165 (15.76%) 27	0 / 5 (0.00%) 0	16 / 110 (14.55%) 17
Hyperthyroidism			

subjects affected / exposed occurrences (all)	11 / 165 (6.67%) 11	0 / 5 (0.00%) 0	6 / 110 (5.45%) 6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 165 (17.58%)	0 / 5 (0.00%)	37 / 110 (33.64%)
occurrences (all)	40	0	54
Back pain			
subjects affected / exposed	22 / 165 (13.33%)	0 / 5 (0.00%)	12 / 110 (10.91%)
occurrences (all)	28	0	13
Groin pain			
subjects affected / exposed	1 / 165 (0.61%)	0 / 5 (0.00%)	1 / 110 (0.91%)
occurrences (all)	1	0	1
Pain in extremity			
subjects affected / exposed	15 / 165 (9.09%)	0 / 5 (0.00%)	7 / 110 (6.36%)
occurrences (all)	15	0	7
Myalgia			
subjects affected / exposed	10 / 165 (6.06%)	0 / 5 (0.00%)	11 / 110 (10.00%)
occurrences (all)	15	0	12
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 165 (6.67%)	0 / 5 (0.00%)	8 / 110 (7.27%)
occurrences (all)	16	0	9
Sinusitis			
subjects affected / exposed	3 / 165 (1.82%)	0 / 5 (0.00%)	6 / 110 (5.45%)
occurrences (all)	3	0	7
Upper respiratory tract infection			
subjects affected / exposed	9 / 165 (5.45%)	1 / 5 (20.00%)	9 / 110 (8.18%)
occurrences (all)	10	1	9
Urinary tract infection			
subjects affected / exposed	14 / 165 (8.48%)	1 / 5 (20.00%)	5 / 110 (4.55%)
occurrences (all)	15	1	15
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	7 / 165 (4.24%)	0 / 5 (0.00%)	8 / 110 (7.27%)
occurrences (all)	10	0	18
Hyperglycaemia			

subjects affected / exposed	3 / 165 (1.82%)	0 / 5 (0.00%)	7 / 110 (6.36%)
occurrences (all)	3	0	9
Hypercalcaemia			
subjects affected / exposed	3 / 165 (1.82%)	0 / 5 (0.00%)	7 / 110 (6.36%)
occurrences (all)	3	0	9
Decreased appetite			
subjects affected / exposed	25 / 165 (15.15%)	0 / 5 (0.00%)	22 / 110 (20.00%)
occurrences (all)	29	0	24

Non-serious adverse events	Cohort A: ccRCC Second Course		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Catheter site pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Pyrexia			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) Wheezing subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		

Weight decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0		

Nausea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Haemorrhoids subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dyspepsia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dry mouth subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Diarrhoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Dry skin subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Rash subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Hyperthyroidism			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Groin pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			

subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2017	Amendment 1 clarified eligibility so that inclusion and exclusion criteria were not overly restrictive, and provided a clear and concise guide to investigators on management of AEs associated with pembrolizumab. Additionally, the amendment allowed enrollment in Cohort B upon local laboratory confirmation of diagnosis, and central laboratory confirmation that the submitted tissue is adequate for central review (previously, central laboratory diagnosis confirmation was required before allocation).
20 November 2017	Amendment 2 updated the dose modification and toxicity management guidelines for pembrolizumab in order to be in alignment with the most current label and safety information for pembrolizumab. The amendment also changed the timing of bone scans at screening (accepting scans that have been performed within 42 days of screening).
02 December 2020	Amendment 3 removed reference to "sub-trial" in the Future Biomarker Research (FBR) sections of the protocol.
09 July 2021	Amendment 4 updated the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported