



## Clinical trial results:

### A Phase II Safety Trial of Nivolumab in Patients with Metastatic Renal Cell Carcinoma Who Have Progressed During or After Prior Systemic Anti-Angiogenic Regimen.

#### Summary

EudraCT number	2015-004117-24
Trial protocol	FR
Global end of trial date	30 June 2021

#### Results information

Result version number	v1 (current)
This version publication date	21 May 2025
First version publication date	21 May 2025

#### Trial information

##### Trial identification

Sponsor protocol code	GETUG-AFU26
-----------------------	-------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03013335
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France,
Public contact	Nourredine AIT RAHMOUNE, UNICANCER, +33 0171936704, n.ait-rahmoune@unicancer.fr
Scientific contact	Nourredine AIT RAHMOUNE, UNICANCER, +33 0171936704, n.ait-rahmoune@unicancer.fr

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	14 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2021
Global end of trial reached?	Yes
Global end of trial date	30 June 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the incidence of high-grade (i.e. Grade 3-4 and Grade 5 of CTCAE v4.0) adverse reactions of interest in patients with metastatic RCC who have progressed during or after receiving at least one prior systemic anti-angiogenic treatment and who are eligible for nivolumab monotherapy.

Protection of trial subjects:

This study was conducted in compliance with the protocol and in accordance with the French national regulatory requirements and the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice (GCP) Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	France: 720
Worldwide total number of subjects	720
EEA total number of subjects	720

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)	353

From 65 to 84 years	360
85 years and over	7

## Subject disposition

### Recruitment

Recruitment details:

From 01-Feb-2016 to 27-Jul-2017, 729 patients were enrolled in the NIVOREN study across 26 centers in France.

The 720 patients who received at least 1 dose of nivolumab were included and analyzed.

### Pre-assignment

Screening details:

Patients were included in the study with mRCC with clear cell component; at least one prior systemic anti-angiogenic treatment; ECOG  $\leq 2$ . Patients will be treated with nivolumab every 2 weeks until disease progression without clinical benefit, unacceptable toxicity, or withdrawal of informed consent, follow-up is planned to last up to 5 years.

### Period 1

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

Blinding implementation details:

NA

### Arms

Arm title	NIVOLUMAB
-----------	-----------

Arm description:

Only one arm in this trial

Treatment: Nivolumab

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

Dosage and administration details:

The dose and schedule of nivolumab in this study was 3 mg/kg every 2 weeks. Infusion of nivolumab were performed in 30 minutes ( $\pm$  5 minutes).

Nivolumab was administered until death, disease progression, unacceptable toxicity or withdrawal of the informed consent.

Number of subjects in period 1	NIVOLUMAB
Started	720
Completed	0
Not completed	720
Physician decision	22
Patient decision	23
End of study/ Progressive disease	495
Response observed by physician/patient/other (Comp	24
Death	41

Other	1
Toxicity/adverse event	114

## Baseline characteristics

### Reporting groups

Reporting group title	Overall periode
-----------------------	-----------------

Reporting group description: -

Reporting group values	Overall periode	Total	
Number of subjects	720	720	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	353	353	
From 65-84 years	360	360	
85 years and over	7	7	
Age continuous			
Units: years			
median	64		
full range (min-max)	22 to 90	-	
Gender categorical			
Units: Subjects			
Female	164	164	
Male	556	556	
ECOG			
Units: Subjects			
Missing data	36	36	
ECOG 0	229	229	
ECOG 1	352	352	
ECOG 2	100	100	
ECOG 3	3	3	
Menopausal status			
Units: Subjects			
Missing data	2	2	
Non-menopause	17	17	
Pre-menopause	4	4	
Menopause	131	131	
Unknown	10	10	
Non applicable	556	556	
Hemoglobin ≤LLN			
Units: Subjects			
NO	324	324	
YES	396	396	
Calcium (corrected) ≥ULN			

Units: Subjects			
Missing data	2	2	
No	553	553	
Yes	165	165	
Neutrophils $\geq$ ULN			
Units: Subjects			
No	645	645	
Yes	75	75	
Platelets >ULN			
Units: Subjects			
No	623	623	
Yes	97	97	
IMDC prognostic/ Score			
Units: Subjects			
Missing data	2	2	
Score = 0	132	132	
Score =1	234	234	
Score =2	171	171	
Score =3	94	94	
Score =4	54	54	
Score =5	25	25	
Score =6	8	8	
IMDC Prognostic			
Units: Subjects			
Missing data	2	2	
Favorable	132	132	
Intermediate	405	405	
Poor	181	181	
Favorable/intermediate versus poor			
IMDC prognostic			
Units: Subjects			
Missing data	2	2	
Favorable/intermediate prognostic	537	537	
Poor prognostic	181	181	

## End points

### End points reporting groups

Reporting group title	NIVOLUMAB
Reporting group description:	
Only one arm in this trial	
Treatment: Nivolumab	

### Primary: Incidence of Grade 3, 4, or 5 ADR

End point title	Incidence of Grade 3, 4, or 5 ADR <sup>[1]</sup>
End point description:	
The primary endpoint of this study was the incidence for high-grade (Grade 3-4 and Grade 5) adverse reactions of interest [i.e. adverse event related to the study treatment (TRAE)]. The adverse reactions of interest were skin, endocrinopathy, gastrointestinal, hepatic, renal, pulmonary, and hypersensitivity adverse events. Due to the frequency of TRAEs observed during the study, safety analyses were done on all TRAEs of grade 3 or more observed by the investigator during the study.	
End point type	Primary
End point timeframe:	
5 years	

#### 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: The primary endpoint of this study was the incidence for high-grade (Grade 3-4 and Grade 5) adverse reactions of interest (i.e. adverse event related to the study treatment). The forms AE from the CRF was used and correspond to the adverse event related to the study treatment judged from investigator. The number of patients with at least one AE of grade  $\geq 3$  related to nivolumab were presented with count, % and 95% confidence interval. Only one arm in this study ,there were no statistical analyses

End point values	NIVOLUMAB			
Subject group type	Reporting group			
Number of subjects analysed	720			
Units: percent of patients				
number (not applicable)				
Patient with at least 1 ADR $\geq$ grade 3	19.9			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS is defined as the time from first dosing date to the date of death. A patient who has not died will be censored at last known date alive. OS will be followed continuously while patients are on the treatment and every 3 months via in-person or phone contact after patients discontinue the study drug.	
End point type	Secondary
End point timeframe:	
5 years	



<b>End point values</b>	NIVOLUMAB			
Subject group type	Reporting group			
Number of subjects analysed	720			
Units: Months				
median (confidence interval 95%)	55.9 (54.4 to 57.3)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)
End point description:	
Objective response rate (ORR) is defined as the number and percentage of patients with a Best Overall Response (BOR) of confirmed complete response (CR) or partial response (PR). Best overall response (BOR) is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurs first. For Patients without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.	
End point type	Secondary
End point timeframe:	
5 years	

<b>End point values</b>	NIVOLUMAB			
Subject group type	Reporting group			
Number of subjects analysed	720			
Units: percent				
median (confidence interval 95%)	21.3 (18.3 to 24.5)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment (up to 5 years).

Adverse event reporting additional description:

For non serious adverse events only treatment-related adverse events (TRAEs) were available.

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

### Dictionary used

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

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

### Reporting groups

Reporting group title	NIVOLUMAB
-----------------------	-----------

Reporting group description:

Of the 729 patients included in the study, 720 patients received at least one dose of nivolumab and were evaluable for the safety analysis. Nine patients did not received the study treatment and were excluded of the safety analysis.

Serious adverse events	NIVOLUMAB		
Total subjects affected by serious adverse events			
subjects affected / exposed	330 / 720 (45.83%)		
number of deaths (all causes)	518		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloblastic leukemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Bone metastases			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain metastases			

subjects affected / exposed	4 / 720 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal metastasis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lentigo maligna melanoma			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lobular breast carcinoma (in situ)			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphangitis carcinomatosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Malignant neoplasm progression			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Metastases to pituitary gland			

subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastatic pain				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myeloid leukaemia				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myeloma				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm progression				
subjects affected / exposed	10 / 720 (1.39%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 7			
Osteolytic bone metastases				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic cancer				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Prostate cancer				
subjects affected / exposed	3 / 720 (0.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Spinocellular carcinom				

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Superficial basal cell carcinoma			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumor compression			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumor progression			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Ischemic stroke			

subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Anasarca			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chronic pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Disease progression			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Drug side effect				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Face edema				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Face oedema				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	7 / 720 (0.97%)			
occurrences causally related to treatment / all	2 / 7			
deaths causally related to treatment / all	0 / 0			
Fever malignant				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	32 / 720 (4.44%)			
occurrences causally related to treatment / all	2 / 33			
deaths causally related to treatment / all	0 / 14			
Hyperthermia				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				

subjects affected / exposed	5 / 720 (0.69%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Thoracic pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Unknown cause of death			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hypertrophy			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthmatoid bronchitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atelectasis			



subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial hemorrhage				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial obstruction				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease exacerbation				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Distress respiratory				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnea				
subjects affected / exposed	11 / 720 (1.53%)			
occurrences causally related to treatment / all	1 / 11			
deaths causally related to treatment / all	0 / 3			
Interstitial lung disease				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial pneumonitis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia interstitial				

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis allergic			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumopathy			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Toxic pneumonitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Clinomania			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Confusion			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Depressive symptom			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychomotor retardation			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Lost weight			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arm fracture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral edema			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug overdose			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Femur fracture			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiation proctitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Scalp injury NOS			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Trauma			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Acute coronary syndrome				
subjects affected / exposed	3 / 720 (0.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cardiomyopathy				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decompensation cardiac				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Heart failure				

subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Myocardial infarction				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial tamponade				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleuropericarditis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic pain				

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervical myelopathy			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epileptic seizure			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Generalized tonic-clonic seizure			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis (right)			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ischemic stroke			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neurologic disorder NOS			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paresthesia lower limb			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Quadriparesis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizures			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			



subjects affected / exposed	7 / 720 (0.97%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Acute anemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anemia			
subjects affected / exposed	7 / 720 (0.97%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 0		
Macrophage activation syndrome			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Posterior uveitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Visual impairment			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Acute hemorrhagic ulcerative colitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute pancreatitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Autoimmune colitis			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Bleeding gastrointestinal			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bleeding rectal			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
C.difficile diarrhoea			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			

subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Colon perforation			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic obstruction			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diarrhea			
subjects affected / exposed	8 / 720 (1.11%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Duodenal stenosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal bleeding			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hemorrhage gastric			

subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemorrhage of digestive tract				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Inguinal hernia				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Lip oedema				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melena				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis biliary			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal bleeding			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small bowel obstruction			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomach hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Subocclusive syndrom			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal bleeding			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Acute cholecystitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cholecystitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cytolysis			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Icterus			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver cholestasis			

subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Obstruction of bile duct			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Portal hypertension			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Bullous dermatitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Dermatosis bullous			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lupus syndrome			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Maculo-papular rash			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Papular rash			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute prerenal failure			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute renal failure			
subjects affected / exposed	9 / 720 (1.25%)		
occurrences causally related to treatment / all	2 / 10		
deaths causally related to treatment / all	0 / 0		
Acute renal insufficiency			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hematuria			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	6 / 720 (0.83%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Autoimmune thyroiditis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decompensated diabetes			



subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Goiter			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Arthralgia multiple			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Costal pain			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammatory arthritis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Leg pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbalgia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar pain			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Osteolytic lesion			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in leg			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain sacroiliac			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyarthrititis			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Polymyalgia rheumatica			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sacroiliac fracture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Vertebral pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess periodontal			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute appendicitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspergillosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			

subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial infection				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchiolitis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter infection				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter related infection				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcus faecalis infection				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epiduritis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Foot infection				

subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemophilus influenza infection				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis E				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection NOS				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection urinary tract				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious pneumonitis				
subjects affected / exposed	7 / 720 (0.97%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 1			
Lung infection				
subjects affected / exposed	5 / 720 (0.69%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	1 / 1			
Parvovirus B19 infection				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				

subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis pneumonia				
subjects affected / exposed	2 / 720 (0.28%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatic abscess				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 720 (0.42%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Sepsis syndrome				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Septic cholangitis				
subjects affected / exposed	1 / 720 (0.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic encephalopathy				

subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Septicemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcus epidermidis infection			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical site infection			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary infection			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic metabolic decompensation			

subjects affected / exposed	2 / 720 (0.28%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypercalcemia			
subjects affected / exposed	26 / 720 (3.61%)		
occurrences causally related to treatment / all	1 / 29		
deaths causally related to treatment / all	0 / 0		
Hyperglycemia			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Hyperkalemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	NIVOLUMAB		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	676 / 720 (93.89%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	8		
Seborrheic keratosis			



subjects affected / exposed occurrences (all)	1 / 720 (0.14%) 2		
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	3		
Hot flush			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	6		
Hypertension			
subjects affected / exposed	8 / 720 (1.11%)		
occurrences (all)	14		
Hypotension			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Varicose vein			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	6		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	185 / 720 (25.69%)		
occurrences (all)	929		
Chest discomfort			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	4		
Chills			
subjects affected / exposed	9 / 720 (1.25%)		
occurrences (all)	12		
Exercise tolerance decreased			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Face edema			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	52 / 720 (7.22%)		
occurrences (all)	234		
Feeling cold			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	3		
General physical health deterioration			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	4		
Generalized edema			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences (all)	5		
Malaise			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Mucosal dryness			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Mucosal inflammation			
subjects affected / exposed	15 / 720 (2.08%)		
occurrences (all)	48		
Edema			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Edema peripheral			
subjects affected / exposed	11 / 720 (1.53%)		
occurrences (all)	29		
Pain			

<p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 720 (0.83%)</p> <p>8</p>		
<p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>15 / 720 (2.08%)</p> <p>24</p>		
<p>Sense of oppression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 720 (0.14%)</p> <p>1</p>		
<p>Xerosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>36 / 720 (5.00%)</p> <p>259</p>		
<p>Immune system disorders</p> <p>Hypersensitivity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 720 (0.83%)</p> <p>8</p>		
<p>Sarcoidosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 720 (0.28%)</p> <p>4</p>		
<p>Reproductive system and breast disorders</p> <p>Balanoposthitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 720 (0.28%)</p> <p>4</p>		
<p>Erectile dysfunction</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 720 (0.28%)</p> <p>13</p>		
<p>Genital erythema</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 720 (0.14%)</p> <p>2</p>		
<p>Genital rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 720 (0.28%)</p> <p>4</p>		
<p>Heavy menstrual bleeding</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 720 (0.14%)</p> <p>1</p>		
<p>Penile edema</p>			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Pruritus genital			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 720 (1.94%)		
occurrences (all)	40		
Dysphonia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	6		
Dyspnea			
subjects affected / exposed	25 / 720 (3.47%)		
occurrences (all)	47		
Dyspnea exertional			
subjects affected / exposed	6 / 720 (0.83%)		
occurrences (all)	20		
Epistaxis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	12		
Hiccups			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Hypersensitivity pneumonitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	3		
Hypoxia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Immune-mediated lung disease			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Interstitial lung disease			

subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	4		
Lung disorder			
subjects affected / exposed	9 / 720 (1.25%)		
occurrences (all)	15		
Organizing pneumonia			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	14		
Oropharyngeal discomfort			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	19		
Pharyngeal paresthesia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Pulmonary embolism			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	6		
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	5		
Sneezing			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Psychiatric disorders			
Affective disorder			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	3		
Insomnia			

subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	5		
Psychomotor retardation			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	3		
Sleep disorder			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 720 (1.53%)		
occurrences (all)	36		
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 720 (1.25%)		
occurrences (all)	26		
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 720 (0.97%)		
occurrences (all)	17		
Blood bilirubin increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Blood creatinine			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	19		
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	13		
Blood potassium increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Blood thyroid stimulating hormone decreased			

subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	11		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	6 / 720 (0.83%)		
occurrences (all)	28		
Blood urea increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	6		
Creatinine renal clearance decreased			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	8		
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 720 (1.25%)		
occurrences (all)	28		
Lipase increased			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	16		
Lymphocyte count decreased			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	4		
Lymphocyte count increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Thyroid hormones decreased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Thyroid hormones increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	12		
Thyroxine free increased			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	5		
Tri-iodothyronine free increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	6 / 720 (0.83%)		
occurrences (all)	8		
Weight increased			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	64		
White blood cell count increased			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Diabetes mellitus inadequate control			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	25		
Gout			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Hypercalcemia			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	11		
Hypercholesterolemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Lip injury			



subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Muscle rupture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Cardiac disorders			
atrial fibrillation			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Atrioventricular block			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Cardiac arrest			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Cardiac failure			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Cyanosis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	6		
Myocarditis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Pleuropericarditis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Tachycardia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Nervous system disorders			
Anosmia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	10		
Burning sensation			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Cerebrovascular accident			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Dysarthria			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	8		
Epilepsy			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	10 / 720 (1.39%)		
occurrences (all)	29		
Hypoesthesia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Ischemic stroke			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Motor dysfunction			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	18		
Myasthenia gravis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Nervous system disorder			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Neuropathy peripheral			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	10		
Paresthesia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	6		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	10		
Sciatica			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Sensorimotor disorder			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	8		
Somnolence			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	22 / 720 (3.06%)		
occurrences (all)	87		
Autoimmune hemolytic anemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		

Eosinophilia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	15		
Leukopenia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	12 / 720 (1.67%)		
occurrences (all)	36		
Neutropenia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	17		
Thrombocytopenia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	40		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Vertigo			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	7		
Vertigo positional			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Blepharitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	4		
Diplopia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	7		
Dry eye			

subjects affected / exposed	8 / 720 (1.11%)		
occurrences (all)	27		
Episcleritis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Eyelid edema			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	7		
Eyelids pruritus			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Keratitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Ocular hyperemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Uveitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	8		
Vision blurred			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Xerophthalmia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	55		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	5		
Abdominal pain			
subjects affected / exposed	10 / 720 (1.39%)		
occurrences (all)	32		
Abdominal pain upper			
subjects affected / exposed	8 / 720 (1.11%)		
occurrences (all)	22		

Aphthous ulcer			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	10		
Aptyalism			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Autoimmune colitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	3		
Colitis			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	25 / 720 (3.47%)		
occurrences (all)	56		
Diarrhea			
subjects affected / exposed	76 / 720 (10.56%)		
occurrences (all)	209		
Dry mouth			
subjects affected / exposed	14 / 720 (1.94%)		
occurrences (all)	110		
Dyspepsia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Frequent bowel movements			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Gastric disorder			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Gastrointestinal hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Hemorrhoids			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		

Large intestine polyp			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Mouth hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	35 / 720 (4.86%)		
occurrences (all)	60		
Oral discomfort			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Oral lichen planus			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	5		
Rectal hemorrhage			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	5		
Stomatitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	17 / 720 (2.36%)		
occurrences (all)	32		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Cholangitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Cholecystitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Cholestasis			

subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	7		
Hepatic cytolysis			
subjects affected / exposed	7 / 720 (0.97%)		
occurrences (all)	16		
Hepatitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Portal hypertension			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	10		
Alopecia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	5		
Dermatitis acneiform			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	9		
Dermatitis bullous			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	17		
Dermatitis diaper			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	13 / 720 (1.81%)		
occurrences (all)	35		
Dyshidrotic eczema			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Eczema			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	19		



Erythema			
subjects affected / exposed	11 / 720 (1.53%)		
occurrences (all)	25		
Erythrosis			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	7		
Hyperhidrosis			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	4		
Hyperkeratosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Lichen planus			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Macule			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Nail disorder			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	29		
Nail toxicity			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Night sweats			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	11		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Pemphigoid			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Photosensitivity reaction			

subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	4		
Plantar erythema			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Prurigo			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	66 / 720 (9.17%)		
occurrences (all)	450		
Psoriasis			
subjects affected / exposed	6 / 720 (0.83%)		
occurrences (all)	52		
Purpura			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	43 / 720 (5.97%)		
occurrences (all)	167		
Rash erythematous			
subjects affected / exposed	7 / 720 (0.97%)		
occurrences (all)	17		
Rash macular			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Rash maculo-papular			
subjects affected / exposed	11 / 720 (1.53%)		
occurrences (all)	17		
Rash papular			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences (all)	37		
Rash pruritic			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	4		
Skin exfoliation			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Skin lesion			
subjects affected / exposed	7 / 720 (0.97%)		
occurrences (all)	26		
Skin reaction			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Skin toxicity			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	4		
Telangiectasia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	4		
Toxic skin eruption			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	7		
Vitiligo			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences (all)	47		
Xeroderma			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences (all)	7		
Chronic kidney disease			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	14		
Proteinuria			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	16		
Renal failure			
subjects affected / exposed	10 / 720 (1.39%)		
occurrences (all)	27		

Renal impairment subjects affected / exposed occurrences (all)	1 / 720 (0.14%) 2		
Endocrine disorders			
Adrenal insufficiency subjects affected / exposed occurrences (all)	8 / 720 (1.11%) 109		
Adrenocortical insufficiency acute subjects affected / exposed occurrences (all)	2 / 720 (0.28%) 3		
Autoimmune thyroiditis subjects affected / exposed occurrences (all)	2 / 720 (0.28%) 9		
Hyperthyroidism subjects affected / exposed occurrences (all)	12 / 720 (1.67%) 39		
Hypophysitis subjects affected / exposed occurrences (all)	1 / 720 (0.14%) 1		
Hypothyroidism subjects affected / exposed occurrences (all)	26 / 720 (3.61%) 163		
Thyroid disorder subjects affected / exposed occurrences (all)	2 / 720 (0.28%) 15		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	61 / 720 (8.47%) 251		
Arthritis subjects affected / exposed occurrences (all)	2 / 720 (0.28%) 8		
Back pain subjects affected / exposed occurrences (all)	12 / 720 (1.67%) 31		
Bone pain			

subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Muscle contracture			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	7 / 720 (0.97%)		
occurrences (all)	16		
Muscular weakness			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	22		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	10		
Musculoskeletal stiffness			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	28 / 720 (3.89%)		
occurrences (all)	82		
Pain in extremity			
subjects affected / exposed	6 / 720 (0.83%)		
occurrences (all)	19		
Pain in jaw			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Plantar fasciitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Polyarthritis			

subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	19		
Polymyalgia rheumatica			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Rheumatoid arthritis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	9		
Sjogren's syndrome			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Spinal pain			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	4		
Systemic lupus erythematosus			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Tendon disorder			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Chorioretinitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	19		
Dermatitis infected			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		

Ecthyma			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Erysipelas			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Folliculitis			
subjects affected / exposed	4 / 720 (0.56%)		
occurrences (all)	26		
Genital infection			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Herpes simplex			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Herpes zoster			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Onychomycosis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	5		
Oral candidiasis			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	3		
Oral herpes			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	3		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		

Pneumonia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Prostatic abscess			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Septic shock			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Skin infection			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	3		
Decreased appetite			
subjects affected / exposed	34 / 720 (4.72%)		
occurrences (all)	90		
Dehydration			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	6		
Diabetes mellitus			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	53		
Hyperglycemia			



subjects affected / exposed	7 / 720 (0.97%)		
occurrences (all)	74		
Hyperkalemia			
subjects affected / exposed	9 / 720 (1.25%)		
occurrences (all)	22		
Hyperuricemia			
subjects affected / exposed	2 / 720 (0.28%)		
occurrences (all)	2		
Hypochloremia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	1		
Hypokalemia			
subjects affected / exposed	3 / 720 (0.42%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	1 / 720 (0.14%)		
occurrences (all)	8		
Hyponatremia			
subjects affected / exposed	7 / 720 (0.97%)		
occurrences (all)	10		
Hypophosphatemia			
subjects affected / exposed	5 / 720 (0.69%)		
occurrences (all)	18		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2016	- Modification of the investigators list
25 April 2016	- Modification of the document of reference for the tumor evaluation - Modification of inclusion and non-inclusion criteria - Modification of the study design scheme - Addition of optional ancillary study - Modification of the flowchart - Correction of typographic errors within the protocol and the synopsis - Modification of the informed consent form - Addition of the co-coordinating investigator - Addition of the statistician's contact information - Modification of the project leader - Modification of the investigators list
10 June 2016	- Modification of the sample size - Redaction of a patient information letter to explain the rational for the new sample size - Modification of the investigators list
05 July 2016	- Modification of the inclusion criteria - Clarification of the statistical analysis plan - Modification of mode of declaration SAE related to disease progression - Modification of the informed consent form - Modification of the investigators list
28 October 2016	- Modification of the sample size - Harmonization of the protocol and inform consent form for treatment after disease progression - Declaration of new center involved in the ancillary study - Modification of the investigators list
26 January 2017	- Extension of the recruitment period - Modification of the investigators list
11 May 2017	- Modification of the investigators list
03 May 2018	- Update of the safety section (protocol and inform consent form) based on the new version of the investigator brochure - New version of investigator brochure - Modification of the investigators list
15 July 2019	- Modification of the informed consent form to inform patient that their personal data will be collected and processed in accordance with the new national data protection legislation: Regulation (EU) 2016/679 (General Data Protection Regulation). - Update of the safety section (inform consent form) based on the new version of the investigator brochure - New version of investigator brochure - Modification of the investigators list
06 November 2020	- Update of the safety section (inform consent form) based on the new version of the investigator brochure - Addition of a new ancillary study including collection of data for bone metastases - New version of investigator brochure - Modification of the investigators list

11 May 2021	<ul style="list-style-type: none"> <li>- The follow up period was reduced for a new end of study planned on June 2021</li> <li>- New version of investigator brochure</li> <li>- Modification of the investigators list</li> </ul>
-------------	--

Notes:

---

## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported