Clinical trial results:
A phase II single arm clinical trial of a Tailored ImmunoTherapy Approach with Nivolumab in subjects with metastatic or advanced Renal Cell Carcinoma

Summary

EudraCT number	2016-002307-26
Trial protocol	DE BE AT CZ ES IT
Global end of trial date	01 October 2021

Results information

Result version number	v1 (current)
This version publication date	05 October 2023
First version publication date	05 October 2023

Trial information

Trial identification

Sponsor protocol code	0216-ASG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02917772
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany, 14057
Public contact	Clinical trial desk of the sponsor, AIO-Studien-gGmbH, +49 308145 34431, info@aio-studien-ggmbh.de
Scientific contact	Clinical trial desk of the sponsor, AIO-Studien-gGmbH, +49 308145 34431, info@aio-studien-ggmbh.de

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 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 October 2021
Global end of trial reached?	Yes
Global end of trial date	01 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the best ORR based on investigator assessment using RECIST 1.1 of the TITAN regimen in untreated (1st line) and pretreated (2nd line) subjects with IMDC intermediate and high risk, advanced RCC with clear cell component

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) ‚Guideline for Good Clinical Practice E6(R1)‘, CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	France: 58
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	207
EEA total number of subjects	194

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)	103
From 65 to 84 years	99
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The first patient was screened on 28-Oct-2016.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	1st line

Arm description: -

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

Dosage and administration details:

Nivolumab Induction Monotherapy:
Subjects received nivolumab 240 mg monotherapy Q2W for 8 dosings (16 weeks).
Treated subjects were evaluated during induction for response according to RECIST 1.1 guidelines at week 8 (± 1 week) and 16 (± 1 week) after first dose.

Tailored Treatment Approach:
Tumor assessment results, together with the investigator's judgement, informed susequent treatment: continuation of nivolumab induction monotherapy, switch to nivolumab/ipilimuab “boost” therapy, or switch to nivolumab maintenance therapy. During "boost" cycles, nivolumab was administered at 3 mg/kg body weight, Q3W.

Nivolumab maintenance: 240 mg monotherapy Q2W

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was only administered during "boost" cycles. Dosage was 1 mg/kg body weight, Q3W.

Arm title	2nd line

Arm description: -

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

Dosage and administration details:

Nivolumab Induction Monotherapy:
Subjects received nivolumab 240 mg monotherapy Q2W for 8 dosings (16 weeks).
Treated subjects were evaluated during induction for response according to RECIST 1.1 guidelines at week 8 (± 1 week) and 16 (± 1 week) after first dose.

Tailored Treatment Approach:
Tumor assessment results, together with the investigator's judgement, informed susequent treatment: continuation of nivolumab induction monotherapy, switch to nivolumab/ipilimuab “boost” therapy, or switch to nivolumab maintenance therapy. During "boost" cycles, nivolumab was administered at 3 mg/kg body weight, Q3W.

Nivolumab maintenance: 240 mg monotherapy Q2W

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was only administered during "boost" cycles. Dosage was 1 mg/kg body weight, Q3W.

Number of subjects in period 1	1st line	2nd line
Started	109	98
Completed	109	98

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	207	207	
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)	103	103	
From 65-84 years	99	99	
85 years and over	5	5	
Age continuous Units: years			
median	65		
full range (min-max)	20 to 87	-	
Gender categorical Units: Subjects			
Female	60	60	
Male	147	147	
Diverse	0	0	
IMDC risk group Units: Subjects			
Favorable	9	9	
Intermediate	147	147	
Poor	51	51	
Karnofsky Performance Status Units: Subjects			
80-100%	170	170	
70%	37	37	

End points

End points reporting groups

Reporting group title	1st line
Reporting group description: -	
Reporting group title	2nd line
Reporting group description: -	

Primary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

The primary endpoint was ORR (based on investigator assessments) among all treated subjects, first line subjects and second line subjects. It was defined as the number of subjects with best overall response (BOR) of CR or PR divided by the number of all treated subjects, first line subjects or second line subjects. Best overall response was defined as the best response designation, as determined by investigator, recorded between the date of first dose and the date of objectively documented immunotherapy resistance per RECIST v1.1 or the date of subsequent therapy, whichever occurred first. For subjects stopping treatment for reasons other than immunotherapy resistance, delayed immunotherapy responses were recorded until subsequent therapy to determine BOR. For subjects without documented immunotherapy-refractory disease or subsequent therapy, all available response designations contributed to the ORR determination.

End point type	Primary

End point timeframe:

ORR was based on best overall response, which was recorded between the date of first dose and the date of objectively documented immunotherapy resistance per RECIST v1.1 (see below for exceptions). Tumor assessment was performed every 8 weeks.

End point values	1st line	2nd line		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Patients	39	31		

Statistical analyses

Statistical analysis title	Statistical analysis of 1st line ORR

Statistical analysis description:

Results for first and second line were analysed separately against respective H0, which was ORR = 25% for each treatment line and referred to nivolumab monotherapy. In other words, the two treatment groups were NOT compared against each other. Subjects in the analysis for 1st line are 109.

Comparison groups	1st line v 2nd line

Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Exact test

Statistical analysis title	Statistical analysis of 2nd line ORR

Statistical analysis description:

Results for first and second line were analysed separately against respective H0, which was ORR = 25% for each treatment line and referred to nivolumab monotherapy. In other words, the two treatment groups were NOT compared against each other. Subjects in the analysis for 2nd line are 98.

Comparison groups	2nd line v 1st line
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.083
Method	Exact test

Secondary: Best overall response (BOR)

End point title	Best overall response (BOR)

End point description:

Best overall response was defined as the best response designation, as determined by investigator, recorded between the date of first dose and the date of objectively documented immunotherapy resistance per RECIST v1.1 or the date of subsequent therapy, whichever occurred first. For subjects stopping treatment for reasons other than immunotherapy resistance, delayed immunotherapy responses were recorded until subsequent therapy to determine BOR. For subjects without documented immunotherapy-refractory disease or subsequent therapy, all available response designations contributed to the BOR determination.

End point type	Secondary

End point timeframe:

Response was recorded between the date of first dose and the date of objectively documented immunotherapy resistance per RECIST v1.1 or the date of subsequent therapy, whichever occurred first. See below for futher exceptions.

End point values	1st line	2nd line		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Patients				
Complete Remission (CR)	8	6		
Partial Remission (PR)	31	25		
Stable Disease (SD)	30	23		
Progressive Disease (PD)	27	35		
Death	11	7		
NE	2	2		

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 both treatment groups, upper limits of confidence intervals were not estimable (NE). The figure 10000000 was entered in lieu.

End point type	Secondary

End point timeframe:

See ORR and BOR

End point values	1st line	2nd line		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Months				
median (confidence interval 95%)	30.7 (12.2 to 10000000)	18.8 (11.2 to 10000000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to immunotherapy resistance (TIR)

End point title	Time to immunotherapy resistance (TIR)

End point description:

Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) was not considered progression for purposes of determining TIR. Subjects who died without a reported prior progression were considered to have progressed on the date of their death. Subjects who did not progress or died were censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die were censored on the date they were registered. Subjects who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. In case of substantial change of anticancer therapy, patients were considered to have progressed on the date of start of therapy.

End point type	Secondary

End point timeframe:

It was defined as the time from first dosing date to the date of documented tumor progression based on investigator assessments (per RECIST 1.1) at the end of 4 “boost” cycles or within 3 months after the last “boost” cycle, or death due to any cause.

End point values	1st line	2nd line		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Months				
median (confidence interval 95%)	22.9 (13.1 to 32.0)	15.5 (12.5 to 25.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

For 2nd line patients, the upper limit of the confidence interval was not estimable (NE). The figure 10000000 was entered in lieu.

End point type	Secondary

End point timeframe:

OS was defined as the time from first dosing date to the date of death. A subject who did not die was censored at last known date alive.

End point values	1st line	2nd line		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Months				
median (confidence interval 95%)	36.1 (27.2 to 46.7)	33.7 (21.6 to 100000000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) was not considered progression for purposes of determining PFS. Subjects who died without a reported prior progression were considered to have progressed on the date of their death. Subjects who did not progress or died were censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die were censored on the date they were registered. Subjects who started any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable tumor assessment prior to or on the date of initiation of

the subsequent anti-cancer therapy. In case of substantial change of anti-cancer therapy, patients were considered to have progressed on the date of start of therapy.

End point type	Secondary

End point timeframe:

PFS was defined as the time from first dosing date to the date of the first documented tumor progression based on investigator assessments (per RECIST 1.1), or death due to any cause.

End point values	1st line	2nd line		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Months				
median (confidence interval 95%)	6.3 (3.7 to 10.1)	3.7 (1.8 to 4.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from first IMP dosing until 100 days after individual end of treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	139 / 207 (67.15%)		
number of deaths (all causes)	102		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bone cancer			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			
subjects affected / exposed	2 / 207 (0.97%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cancer pain			

subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm progression			
subjects affected / exposed	35 / 207 (16.91%)		
occurrences causally related to treatment / all	0 / 39		
deaths causally related to treatment / all	0 / 35		
Adenocarcinoma of salivary gland			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemodynamic instability			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Renal lesion excision			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 207 (1.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Malaise			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pain				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	3 / 207 (1.45%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	4 / 207 (1.93%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cardiac death				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysacusis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pleural effusion				
subjects affected / exposed	4 / 207 (1.93%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	4 / 207 (1.93%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Psychiatric disorders				
Delirium				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood potassium increased				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accidental overdose				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				

subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carotid artery stenosis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal injury				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial fibrillation				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				

subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pericardial effusion				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	3 / 207 (1.45%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 1			
Epilepsy				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				

subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Paraparesis				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subarachoid haemorrhage				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Facial paresis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Parkinson's disease				

subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological decompensation				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	3 / 207 (1.45%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	9 / 207 (4.35%)			
occurrences causally related to treatment / all	7 / 9			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Intestinal obstruction				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intussusception				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vomiting				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune pancreatitis				

subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-mediated enterocolitis			
subjects affected / exposed	13 / 207 (6.28%)		
occurrences causally related to treatment / all	14 / 16		
deaths causally related to treatment / all	0 / 0		
Obstructive pancreatitis			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholangitis			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-mediated hepatitis			
subjects affected / exposed	2 / 207 (0.97%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pemphigoid			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			

subjects affected / exposed	2 / 207 (0.97%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 207 (0.97%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	2 / 207 (0.97%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	7 / 207 (3.38%)		
occurrences causally related to treatment / all	3 / 7		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	5 / 207 (2.42%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	7 / 207 (3.38%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Bone pain				
subjects affected / exposed	4 / 207 (1.93%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
myalgia				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Epididymitis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	12 / 207 (5.80%)			
occurrences causally related to treatment / all	3 / 14			
deaths causally related to treatment / all	0 / 3			
Pneumonia pneumococcal				

subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 207 (1.93%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			
Urinary tract infection				
subjects affected / exposed	5 / 207 (2.42%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 207 (0.97%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Streptococcal sepsis				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes ophthalmic				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal infection				
subjects affected / exposed	1 / 207 (0.48%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholangitis infective				

subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	3 / 207 (1.45%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	200 / 207 (96.62%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 207 (8.21%)		
occurrences (all)	19		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	73 / 207 (35.27%)		
occurrences (all)	121		
Chest pain			
subjects affected / exposed	11 / 207 (5.31%)		
occurrences (all)	12		
Fatigue			

subjects affected / exposed	55 / 207 (26.57%)		
occurrences (all)	67		
Mucosal inflammation			
subjects affected / exposed	15 / 207 (7.25%)		
occurrences (all)	17		
Oedema peripheral			
subjects affected / exposed	26 / 207 (12.56%)		
occurrences (all)	32		
Pyrexia			
subjects affected / exposed	30 / 207 (14.49%)		
occurrences (all)	39		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	50 / 207 (24.15%)		
occurrences (all)	71		
Dyspnoea			
subjects affected / exposed	26 / 207 (12.56%)		
occurrences (all)	38		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 207 (6.76%)		
occurrences (all)	15		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 207 (10.14%)		
occurrences (all)	27		
Amylase increased			
subjects affected / exposed	24 / 207 (11.59%)		
occurrences (all)	28		
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 207 (8.21%)		
occurrences (all)	28		
Blood creatinine increased			
subjects affected / exposed	21 / 207 (10.14%)		
occurrences (all)	24		
Lipase increased			

subjects affected / exposed	26 / 207 (12.56%)		
occurrences (all)	34		
Weight decreased			
subjects affected / exposed	15 / 207 (7.25%)		
occurrences (all)	16		
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 207 (7.73%)		
occurrences (all)	24		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 207 (14.98%)		
occurrences (all)	34		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	23 / 207 (11.11%)		
occurrences (all)	27		
Constipation			
subjects affected / exposed	35 / 207 (16.91%)		
occurrences (all)	48		
Diarrhoea			
subjects affected / exposed	73 / 207 (35.27%)		
occurrences (all)	121		
Dry mouth			
subjects affected / exposed	11 / 207 (5.31%)		
occurrences (all)	12		
Nausea			
subjects affected / exposed	37 / 207 (17.87%)		
occurrences (all)	49		
Vomiting			
subjects affected / exposed	29 / 207 (14.01%)		
occurrences (all)	40		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	17 / 207 (8.21%)		
occurrences (all)	21		
Erythema			

subjects affected / exposed	17 / 207 (8.21%)		
occurrences (all)	18		
Pruritus			
subjects affected / exposed	66 / 207 (31.88%)		
occurrences (all)	99		
Rash			
subjects affected / exposed	53 / 207 (25.60%)		
occurrences (all)	77		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	16 / 207 (7.73%)		
occurrences (all)	17		
Hypothyroidism			
subjects affected / exposed	20 / 207 (9.66%)		
occurrences (all)	20		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	54 / 207 (26.09%)		
occurrences (all)	92		
Back pain			
subjects affected / exposed	43 / 207 (20.77%)		
occurrences (all)	56		
Bone pain			
subjects affected / exposed	11 / 207 (5.31%)		
occurrences (all)	12		
Musculoskeletal pain			
subjects affected / exposed	27 / 207 (13.04%)		
occurrences (all)	31		
Myalgia			
subjects affected / exposed	16 / 207 (7.73%)		
occurrences (all)	22		
Pain in extremity			
subjects affected / exposed	18 / 207 (8.70%)		
occurrences (all)	19		
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	24 / 207 (11.59%)		
occurrences (all)	27		
Urinary tract infection			
subjects affected / exposed	14 / 207 (6.76%)		
occurrences (all)	14		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	13 / 207 (6.28%)		
occurrences (all)	17		
Hyperglycaemia			
subjects affected / exposed	16 / 207 (7.73%)		
occurrences (all)	24		
Hyperkalaemia			
subjects affected / exposed	12 / 207 (5.80%)		
occurrences (all)	18		
Hyperuricaemia			
subjects affected / exposed	12 / 207 (5.80%)		
occurrences (all)	23		
Decreased appetite			
subjects affected / exposed	57 / 207 (27.54%)		
occurrences (all)	76		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2016	- Addition of the term legally acceptable representatives when signing the consent form in the inclusion criteria a) and b) and correspondingly in the exclusion criterion "o) Subjects who are unable to consent because they do not understand the nature, significance and implications of the clinical trial and therefore cannot form a rational intention in the light of the facts and who don't have a legally acceptable representative". The possibility of a legally acceptabele representative giving consent to participation in the clinical trial was already provided for in the approved protocol version 1.1. of 21.6.2016 and was taken into account accordingly in the patient information and consent forms. In order to ensure completeness and accuracy, the wording of the inclusion criterion was adapted accordingly. - Revision of the exclusion criterion "History of severe hypersensitivity reaction to any monoclonal antibody or any constituent of the product" according to the deficiency letter of the PEI (enclosed with the initial application). - Addition of the exclusion criterion "Participation in another clinical intervention trial 30 days prior to registration". - According to RECIST 1.1 guidelines, it is recommended for single-arm studies with the endpoint Objective Remission Rate (ORR) to conduct a confirmatory tumour assessment after 28 days at the earliest in case of a response (partial response or complete response). The performance of the confirmatory scan was not included in protocol version 1.1. A confirmatory scan after 6 weeks (+1 week) was added to all necessary sections of the protocol in version 2.0 to ensure that the protocol complies with the applicable requirements for response evaluation according to RECIST 1.1.
27 July 2017	- The definition of a new baseline was added in accordance with another protocol of the sponsor and the same IMPs (Eudra-CT: 2016-004857-33). It was necessary to make clear that a new baseline according to RECIST 1.1 has to be defined before "boost" initiation based on the last prior tumor assessment. To state this more precisely in the respective sections was necessary to ensure a correct treatment decision. The determination of the ORR was specified to be related to the baseline tumor assessment prior to first dose. A new baseline has to be defined before "boost" initiation for a correct recording of response or therapy failure. This is necessary to assess the effect of "boost" and subsequent treatment decisions. In addition, chapter 3.2 Post Study Access to Therapy was clarified in line with the approval of the investigational medicinal products and taking patient safety into account. - In Chapter 3.5 Discontinuation of Subjects Following any Treatment with Study Drug, the criterion of rapid progression was included as a discontinuation criterion, depending on the decision of the investigator. - Specification of physical examinations in screening (Table 5.1-1) and safety assessments (table 5.1-2): "physical examination: Includes: general appearance; head, eyes, nose…". - New information/instructions on the treatment of adverse events and permanent discontinuation of treatment with study drug(s) were added and the time period for the collection and reporting of SAEs (from the first dose of study drug and up to 100 days after the last dose of study drug(s)) was extended in line with another clinical trial of the sponsor with the same study drug(s). The time period for the collection and reporting of SAEs (from the first dose of the investigational product and until 100 days after the last dose of the investigational product(s)) is clarified.

24 May 2018	Due to delays in starting up the trial in international countries the planned number of 200 patients was not reached after 18 months. Therefore, the recruitment period was prolonged for 6 months to enable that patients can be included in all 8 participating countries. Total study duration was prolonged accordingly. Besides the prolongation of study duration, protocol was specified and adjusted considering experiences from the practice, especially for evaluation of tumor assessments within the planned time frame and the exact timing of treatment doses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported