Clinical trial results:
A Phase 2, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Standard of Care in Subjects with Previously Untreated and Advanced (unresectable or metastatic) non-clear Cell Renal Cell Carcinoma

Summary

EudraCT number	2016-000706-12
Trial protocol	DE AT NL CZ BE ES GB FR IT
Global end of trial date	23 November 2023

Results information

Result version number	v1 (current)
This version publication date	07 February 2025
First version publication date	07 February 2025

Trial information

Trial identification

Sponsor protocol code	SUNNIFORECAST

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03075423
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Goethe University Frankfurt
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt/Main, Germany, 60590
Public contact	Dr. Nicola Gökbuget, Goethe University Frankfurt, 0049 6963016366, goekbuget@em.uni-frankfurt.de
Scientific contact	Dr. Nicola Gökbuget, Goethe University Frankfurt, 0049 6963016366, goekbuget@em.uni-frankfurt.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	29 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2023
Global end of trial reached?	Yes
Global end of trial date	23 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the of OS rate at 12 months of Nivolumab combined with Ipilimumab to Standard of Care in patients with previously untreated and advanced non-clear cell RCC.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with European Union Directive 2001/20/EC. The protocol and any amendments and the subject informed consent document received approval/favorable opinion from all involved national Compentent Authorities and/or from Institutional Review Boards/Independent Ethics Committees (IRB/IEC), as appropriate.
All potential serious breaches of the study protocol had to be reported to the sponsor immediately. A serious breach was defined as a breach of the conditions and principles of GCP in connection with the study or the protocol, which was likely to affect, to a significant degree, the safety or physical or mental integrity of the participants of the study or the scientific value of the study.
Informed consent had to be obtained before the performance of any protocol related procedures that were not part of normal patient care. Investigators had to ensure that subjects were clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 44
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	France: 101
Country: Number of subjects enrolled	Germany: 86
Worldwide total number of subjects	316
EEA total number of subjects	294

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)	176
From 65 to 84 years	139
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In total, 372 patients were screened, of which 316 were enrolled, and 56 were screening failures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivo/Ipi

Arm description:

Four cycles of run-in treatment with combined nivolumab and ipilimumab was followed by nivolumab monotherapy maintenance treatment.

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

Dosage and administration details:

Nivolumab was administered during four cycles of run-in treatment every three weeeks in combination with ipilimumab. During the run-in phase, nivolumab was dosed at 3 mg/kg body weight. After run-in, nivolumab was administered at a fixed dose of 240 mg every two weeks, or at 480 mg every four weeks. Treatment was to continue until disease progression (under certain conditions, treatment beyond progression was allowed), unacceptable toxicity, withdrawal of consent, or death.

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

Dosage and administration details:

Ipilimumab was administered during four cycles of run-in treatment every three weeeks in combination with nivolumab. Ipilimumab was dosed at 1 mg/kg body weight. Treatment was to continue until disease progression (under certain conditions, treatment beyond progression was allowed), unacceptable toxicity, withdrawal of consent, or death.

Arm title	Standard-of-care (SOC)

Arm description:

At the beginnig of the study, sunitinib was the only SOC comparator to be used as per protocol. The protocol was then amended to allow for all authorized treatment regimens, to be allocated to patients as per standard-of-care and by discretion of the investigator.
Of the 143 patients treated in the SOC arm, 112 (78.3%) received sunitinib, 10 (7.0%) cabozantinib, 1 (0.7%) pazopanib, 1 (0.7%) lenvatinib 15 (10.5%) axitinib in combination with a checkpoint inhibitor, 2 (1.4%) cabozantinib combined with nivolumab, and one patient each (0.7%, respectively) received cisplatin with gemcitabine, and MVAC (methotrexate, vinblastine, doxorubicin and cisplatin).

Arm type	standard-of-care

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Nivo/Ipi	Standard-of-care (SOC)
Started	157	152
Completed	156	143
Not completed	1	9
Consent withdrawn by subject	-	5
Patient's wish	-	2
Other	1	1
Study ended by sponsor	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 316 enrolled patients, 7 were not randomized. The full analysis set for this study, therefore, contains the 309 randomized participants, and baseline characteristics are reported for this set.

Baseline characteristics

Reporting groups	
Reporting group title	Nivo/Ipi
Reporting group description:	
Four cycles of run-in treatment with combined nivolumab and ipilimumab was followed by nivolumab monotherapy maintenance treatment.	
Reporting group title	Standard-of-care (SOC)
Reporting group description:	
At the beginnig of the study, sunitinib was the only SOC comparator to be used as per protocol. The protocol was then amended to allow for all authorized treatment regimens, to be allocated to patients as per standard-of-care and by discretion of the investigator. Of the 143 patients treated in the SOC arm, 112 (78.3%) received sunitinib, 10 (7.0%) cabozantinib, 1 (0.7%) pazopanib, 1 (0.7%) lenvatinib 15 (10.5%) axitinib in combination with a checkpoint inhibitor, 2 (1.4%) cabozantinib combined with nivolumab, and one patient each (0.7%, respectively) received cisplatin with gemcitabine, and MVAC (methotrexate, vinblastine, doxorubicin and cisplatin).	

Reporting group values	Nivo/Ipi	Standard-of-care (SOC)	Total
Number of subjects	157	152	309
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	61.4	64.0	
full range (min-max)	18.8 to 81.8	19.4 to 86.2	-
Gender categorical Units: Subjects			
Female	45	45	90
Male	112	107	219
Histology			
Histology as registered in the eCRF for stratified randomization. Per default, results from central pathology assessments were to be used. However, if central pathology results were pending at the time of randomization, local pathology results were used instead.			
Units: Subjects			
Papillary	99	91	190
Non-papillary	58	60	118
Missing	0	1	1
IMDC Score			
Prognosis according to the International Metastatic Renal-Cell Carcinoma Database Consortium Score			
Units: Subjects			
Favourable	39	35	74
Intermediate	79	81	160
Poor	39	36	75

End points

End points reporting groups

Reporting group title	Nivo/Ipi

Reporting group description:

Four cycles of run-in treatment with combined nivolumab and ipilimumab was followed by nivolumab monotherapy maintenance treatment.

Reporting group title	Standard-of-care (SOC)

Reporting group description:

At the beginnig of the study, sunitinib was the only SOC comparator to be used as per protocol. The protocol was then amended to allow for all authorized treatment regimens, to be allocated to patients as per standard-of-care and by discretion of the investigator.
Of the 143 patients treated in the SOC arm, 112 (78.3%) received sunitinib, 10 (7.0%) cabozantinib, 1 (0.7%) pazopanib, 1 (0.7%) lenvatinib 15 (10.5%) axitinib in combination with a checkpoint inhibitor, 2 (1.4%) cabozantinib combined with nivolumab, and one patient each (0.7%, respectively) received cisplatin with gemcitabine, and MVAC (methotrexate, vinblastine, doxorubicin and cisplatin).

Primary: OS rate after 12 months

End point title	OS rate after 12 months

End point description:

End point type	Primary

End point timeframe:

Overall survival was defined as the time from randomization to the date of death from any cause. OS rate at 12 months was defined as the proportion of patients alive at the milestone of 12 months after randomization.

End point values	Nivo/Ipi	Standard-of-care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	152		
Units: Percentage				
number (confidence interval 95%)	78.25 (70.93 to 83.94)	68.33 (59.98 to 75.30)		

Statistical analyses

Statistical analysis title	Superiority of OS12 rate

Statistical analysis description:

The statstical hypothesis test was a standard z test for comparison of 2 survival rates using Greenwood's formula.

Comparison groups	Nivo/Ipi v Standard-of-care (SOC)

Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0263
Method	see 'Analysis description'

Secondary: OS rates after 6 and 18 months

End point title	OS rates after 6 and 18 months

End point description:

End point type	Secondary

End point timeframe:

Overall survival was defined as the time from randomization to the date of death from any cause. OS milestone rates were defined as the proportion of patients alive at the milestone of 6 and 18 months after randomization.

End point values	Nivo/Ipi	Standard-of-care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	152		
Units: Percentage				
number (confidence interval 95%)				
OS rate at 6 months	91.08 (85.40 to 94.62)	85.41 (78.50 to 90.23)		
OS rate at 18 monhts	66.69 (58.71 to 73.49)	60.22 (51.61 to 67.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median OS

End point title	Median OS

End point description:

For subjects that were alive, their survival time was to be censored at the date of last contact (“last known alive date”). Overall survival was to be censored for subjects at the date of randomization if they were randomized but had no follow-up.

End point type	Secondary

End point timeframe:

Overall survival was defined as the time from randomization to the date of death from any cause.

End point values	Nivo/Ipi	Standard-of-care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	152		
Units: Months				
median (confidence interval 95%)	33.22 (23.37 to 40.76)	25.22 (18.81 to 33.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS rates after 6, 12, and 18 months

End point title	PFS rates after 6, 12, and 18 months

End point description:

The following censoring rules were to be applied for the primary definition of PFS:
- Subjects who did not progress were to be 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 to be censored on their date of randomization.
- Subjects who received subsequent systemic anti-cancer therapy prior to documented progression were to be censored at the date of the last tumor assessment prior to the initiation of the new therapy.

End point type	Secondary

End point timeframe:

PFS was specified as the time between the date of randomization and the first date of documented progression, based on assessment by Independent Radiology Review Committee (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first.

End point values	Nivo/Ipi	Standard-of-care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	152		
Units: Percentage				
number (confidence interval 95%)				
6-month PFS rate	45.25 (37.12 to 53.02)	46.60 (37.86 to 53.02)		
12-month PFS rate	28.81 (21.39 to 36.64)	30.37 (22.50 to 38.60)		
18-month PFS rate	23.44 (16.50 to 31.10)	20.55 (13.81 to 28.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS

End point title	Median PFS

End point description:

The following censoring rules were to be applied for the primary definition of PFS:
- Subjects who did not progress were to be 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 to be censored on their date of randomization.
- Subjects who received subsequent systemic anti-cancer therapy prior to documented progression were to be censored at the date of the last tumor assessment prior to the initiation of the new therapy.

End point type	Secondary

End point timeframe:

PFS was specified as the time between the date of randomization and the first date of documented progression, based on IRRC assessment (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first.

End point values	Nivo/Ipi	Standard-of-care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	152		
Units: Months				
median (confidence interval 95%)	5.36 (3.17 to 7.80)	5.65 (5.39 to 8.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiologic response

End point title	Radiologic response

End point description:

For patients without a documented end of treatment date, the date of last infusion (experimental arm) respective the last date of the last cycles (SOC arm) was used to determine the end of treatment. All tumor assessments until 35 days after the end of treatment were included in the analysis of best overall response.

End point type	Secondary

End point timeframe:

Radiologic response was assessed by the clinicians using the RECIST 1.1 criteria for tumor response at baseline and the every 12 weeks as long as the patient was under study treatment.

End point values	Nivo/Ipi	Standard-of-care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: Patients				
Complete Response	10	2		
Partial Response	31	22		
Stable Disease	41	77		
Progressive Disease	43	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

The objective response rate was defined as the proportion of randomized subjects who achieve a best response of complete remission (CR) or partial remission (PR) using the RECIST1.1 criteria.

End point type	Secondary

End point timeframe:

Radiologic response was assessed by the clinicians using the RECIST criteria for tumor response at baseline and the every 12 weeks as long as the patient was under study treatment.

End point values	Nivo/Ipi	Standard-of-care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	124		
Units: Patients				
Patients with objective response	41	24		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from start of study drug treatment until 30 days after discontinuation of dosing. Adverse events occurring before administration of study drug were considered and documented as baseline signs and symptoms.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Experimental (Nivo-Ipi)
Reporting group description: -	
Reporting group title	Standard-of-care

Reporting group description: -

Serious adverse events	Experimental (Nivo-Ipi)	Standard-of-care	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 156 (48.08%)	55 / 152 (36.18%)	
number of deaths (all causes)	93	90	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms - other			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			
subjects affected / exposed	1 / 156 (0.64%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures - other			

subjects affected / exposed	1 / 156 (0.64%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 156 (1.28%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	4 / 156 (2.56%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	2 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and asc - other			
subjects affected / exposed	2 / 156 (1.28%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malaise			
subjects affected / exposed	0 / 156 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 156 (1.28%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Autoimmue disorder			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adult respiratory distress syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnea			
subjects affected / exposed	3 / 156 (1.92%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	1 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Epistaxis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngopharyngeal dysesthesia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 156 (1.92%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders - other			
subjects affected / exposed	2 / 156 (1.28%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Confusion			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CPK increased			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations - other			
subjects affected / exposed	1 / 156 (0.64%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 156 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell decreased			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 156 (0.64%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders - other			
subjects affected / exposed	3 / 156 (1.92%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Heart failure			
subjects affected / exposed	1 / 156 (0.64%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dysarthria			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders - other			
subjects affected / exposed	1 / 156 (0.64%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	

Neuralgia			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischemic attacks			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 156 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders - other			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders - other			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	6 / 156 (3.85%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ascites			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis			
subjects affected / exposed	5 / 156 (3.21%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation			
subjects affected / exposed	3 / 156 (1.92%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	3 / 156 (1.92%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagitis			

subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders - other			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 156 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders - other			
subjects affected / exposed	4 / 156 (2.56%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Portal vein throbosis			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Bullous dermatitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders - other			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 156 (0.00%)	6 / 152 (3.95%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic kidney disease			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis noninfective			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal hemorrhage			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 156 (0.64%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	3 / 156 (1.92%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders - other			

subjects affected / exposed	3 / 156 (1.92%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 156 (0.64%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 156 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders - other			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Biliary tract infection			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - other			
subjects affected / exposed	3 / 156 (1.92%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 156 (2.56%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 156 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcemia			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			
subjects affected / exposed	2 / 156 (1.28%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	0 / 156 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders - other			
subjects affected / exposed	1 / 156 (0.64%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental (Nivo-Ipi)	Standard-of-care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	152 / 156 (97.44%)	140 / 152 (92.11%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 156 (16.67%)	20 / 152 (13.16%)	
occurrences (all)	29	24	
Creatinine increased			

subjects affected / exposed	8 / 156 (5.13%)	12 / 152 (7.89%)	
occurrences (all)	9	13	
Lipase increased			
subjects affected / exposed	8 / 156 (5.13%)	9 / 152 (5.92%)	
occurrences (all)	9	11	
Neutrophil count decreased			
subjects affected / exposed	2 / 156 (1.28%)	16 / 152 (10.53%)	
occurrences (all)	2	24	
Platelet count decreased			
subjects affected / exposed	3 / 156 (1.92%)	24 / 152 (15.79%)	
occurrences (all)	12	29	
Serum amylase increased			
subjects affected / exposed	9 / 156 (5.77%)	4 / 152 (2.63%)	
occurrences (all)	9	6	
Weight loss			
subjects affected / exposed	12 / 156 (7.69%)	15 / 152 (9.87%)	
occurrences (all)	12	15	
White blood cell decreased			
subjects affected / exposed	0 / 156 (0.00%)	7 / 152 (4.61%)	
occurrences (all)	0	10	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 156 (6.41%)	57 / 152 (37.50%)	
occurrences (all)	12	68	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 156 (8.33%)	13 / 152 (8.55%)	
occurrences (all)	17	13	
Insomnia			
subjects affected / exposed	9 / 156 (5.77%)	10 / 152 (6.58%)	
occurrences (all)	9	10	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	24 / 156 (15.38%)	28 / 152 (18.42%)	
occurrences (all)	30	35	
General disorders and administration site conditions			

Edema face			
subjects affected / exposed	0 / 156 (0.00%)	11 / 152 (7.24%)	
occurrences (all)	0	13	
Edema limbs			
subjects affected / exposed	12 / 156 (7.69%)	7 / 152 (4.61%)	
occurrences (all)	15	10	
Fatigue			
subjects affected / exposed	69 / 156 (44.23%)	91 / 152 (59.87%)	
occurrences (all)	91	117	
Pain			
subjects affected / exposed	16 / 156 (10.26%)	20 / 152 (13.16%)	
occurrences (all)	21	22	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 156 (8.97%)	20 / 152 (13.16%)	
occurrences (all)	16	22	
Constipation			
subjects affected / exposed	31 / 156 (19.87%)	26 / 152 (17.11%)	
occurrences (all)	38	29	
Diarrhea			
subjects affected / exposed	43 / 156 (27.56%)	71 / 152 (46.71%)	
occurrences (all)	63	123	
Dry mouth			
subjects affected / exposed	11 / 156 (7.05%)	7 / 152 (4.61%)	
occurrences (all)	11	9	
Dysgeusia			
subjects affected / exposed	6 / 156 (3.85%)	41 / 152 (26.97%)	
occurrences (all)	7	44	
Gastroesophageal reflux disease			
subjects affected / exposed	5 / 156 (3.21%)	25 / 152 (16.45%)	
occurrences (all)	5	28	
Mucositis oral			
subjects affected / exposed	7 / 156 (4.49%)	55 / 152 (36.18%)	
occurrences (all)	8	68	
Nausea			

subjects affected / exposed	32 / 156 (20.51%)	46 / 152 (30.26%)	
occurrences (all)	41	70	
Vomiting			
subjects affected / exposed	16 / 156 (10.26%)	24 / 152 (15.79%)	
occurrences (all)	19	24	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	22 / 156 (14.10%)	21 / 152 (13.82%)	
occurrences (all)	23	22	
Dyspnea			
subjects affected / exposed	17 / 156 (10.90%)	18 / 152 (11.84%)	
occurrences (all)	19	22	
Epistaxis			
subjects affected / exposed	1 / 156 (0.64%)	15 / 152 (9.87%)	
occurrences (all)	1	19	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	13 / 156 (8.33%)	10 / 152 (6.58%)	
occurrences (all)	14	11	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 156 (1.92%)	40 / 152 (26.32%)	
occurrences (all)	3	58	
Pruritus			
subjects affected / exposed	45 / 156 (28.85%)	4 / 152 (2.63%)	
occurrences (all)	51	4	
Rash maculo-papular			
subjects affected / exposed	23 / 156 (14.74%)	8 / 152 (5.26%)	
occurrences (all)	25	8	
Skin hypopigmentation			
subjects affected / exposed	0 / 156 (0.00%)	8 / 152 (5.26%)	
occurrences (all)	0	8	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	7 / 156 (4.49%)	9 / 152 (5.92%)	
occurrences (all)	8	10	
Urinary tract infection			

subjects affected / exposed	5 / 156 (3.21%)	7 / 152 (4.61%)	
occurrences (all)	5	8	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	25 / 156 (16.03%)	3 / 152 (1.97%)	
occurrences (all)	27	3	
Hypothyroidism			
subjects affected / exposed	21 / 156 (13.46%)	34 / 152 (22.37%)	
occurrences (all)	21	34	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	19 / 156 (12.18%)	16 / 152 (10.53%)	
occurrences (all)	20	17	
Myalgia			
subjects affected / exposed	11 / 156 (7.05%)	8 / 152 (5.26%)	
occurrences (all)	13	12	
Pain in extremity			
subjects affected / exposed	6 / 156 (3.85%)	8 / 152 (5.26%)	
occurrences (all)	6	8	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	22 / 156 (14.10%)	33 / 152 (21.71%)	
occurrences (all)	23	34	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2017	Protocol version 3.0 introduced a substantial change in the allowed treatment regimens in the comparator arm. In the initial protocol, the only drug to be used in the comparator arm was sunitinib. This was amended to allow all authorized standard-of-care agents. The reason behind this extension of comparator options was to adapt the study to the clinical reality, especially in European countries other than Germany, and to thus facilitate recruitment and the participation of study sites from different countries. However, the use of immune checkpoint inhibitors was precluded by the exclusion criteria.
02 June 2020	Protocol version 4.0 removed the restriction of using regimens containing immune checkpoint inhibitors in the SOC arm. Moreover, for the experimental arm, the option of using fixed doses of nivolumab at 480 mg 4-weekly during maintenance therapy was introduced. Moreover, instructions for toxicity management were updated, and corrections, edits for consistency and clarifications were introduced.
20 July 2020	With protocol version 4.1 the time point for the interim analysis was amended. Initially, interim analysis was to take place after 2/3 of the planned patient number had been accrued. This was changed to conducting the interim analysis after inclusion of 50% of the planned patient number. The amendment also included the correction of minor errors and updates to study results in the introduction.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported