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

Summary

EudraCT number	2016-004857-33
Trial protocol	DE AT
Global end of trial date	17 February 2023

Results information

Result version number	v1 (current)
This version publication date	08 February 2025
First version publication date	08 February 2025

Trial information

Trial identification

Sponsor protocol code	0416-ASG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03219775
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany,
Public contact	Clinical trial desk of the sponsor, AIO-Studien-gGmbH, +49 30814534431, info@aio-studien-ggmbh.de
Scientific contact	Clinical trial desk of the sponsor, AIO-Studien-gGmbH, +49 30814534431, 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	25 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2023
Global end of trial reached?	Yes
Global end of trial date	17 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to be measured by the primary endpoint of ORR (based on investigator assessments). The ORR was based on investigator assessment using RECIST 1.1 of the TITAN-TCC regimen in untreated (1st line) and platinum-based pretreated (2nd and 3rd line) subjects with metastatic or surgically unresectable TCC

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	14 July 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	Austria: 46
Country: Number of subjects enrolled	Germany: 123
Worldwide total number of subjects	169
EEA total number of subjects	169

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)	57
From 65 to 84 years	112
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The first patient was recruited on 14-Jul-2017; last patient last visit was on 17-Feb-2023.
Recruitment of first-line patients was paused by the Sponsor on 25-Jan-2019 and definitively terminated on 06-Jan-2020.

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	Cohort 1, 1st line

Arm description:

Patients who received 1st-line treatment under protocol version 3.0. Under this version, nivolumab was given at 3 mg/kg and ipilimumab at 1 mg/kg during the first boost treatment, and nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg during the second boost treatment.
Of the 42 patients in this cohort, 14 continued nivo mono maintenance after induction, 17 received a first boost treatment, and 11 discontinued treatment. Of the 17 patients who received a first boost treatment, 6 could switch to nivo maintenance, 7 continued with a second boost treatment, and 4 discontinued treatment. Of the 7 patients who received a second boost treatment, 4 could switch to nivo maintenance, two discontinued treatment due to adverse events, and 1 was found immunotherapy resistant.

Arm type	Experimental
Investigational medicinal product name	Nivolumab 240 mg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a fixed dose of 240 mg IV for four cycles of induction treatment (Q2W). Subsequently, tumor assessment according to RECIST 1.1 was carried out. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, treatment was switched to a 'boost' treatment of combined nivolumab and ipilimumab. If patients developed progressive disease at any time point during maintenance therapy, treatment was also switched to a 'boost' using combined nivolumab and ipilimumab.

Investigational medicinal product name	Nivolumab 3 mg/kg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a dose of 3 mg/kg body weight during the first 'boost' treatment in cohort 1 for two cycles (Q2W) together with ipilimumab at 1 mg/kg. Subsequently, tumor assessment according to RECIST 1.1 was carried out. In case of complete or partial remission, treatment with nivolumab at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, patients received a second 'boost' treatment.

Investigational medicinal product name	Ipilimumab 1 mg/kg
Investigational medicinal product code	
Other name	Yervoy

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was administered at a dose of 1 mg/kg body weight during the first 'boost' treatment in cohort 1 for two cycles (Q2W) together with nivolumab at 3 mg/kg. Subsequently, tumor assessment according to RECIST 1.1 was carried out. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, patients received a second 'boost' treatment.

Investigational medicinal product name	Nivolumab 1 mg/kg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a dose of 1 mg/kg body weight during the second 'boost' treatment in cohort 1, and in both the first and the second 'boost' treatment in cohort 2 together with ipilimumab at 3 mg/kg. 'Boost' treatment was to be administered for two cycles (Q2W).
Subsequent tumor assessment according to RECIST 1.1 informed the next treatment. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, eligible patients received a second 'boost' treatment. Patients with stable disease and ineligible for further boosts treatment were also switched to nivolumab maintenance treatment at 240 mg fixed dose. Patients with progressive disease and ineligible for further 'boost' treatment were decleared as immunotherapy resistant, and discontiued treatment within the study.

Investigational medicinal product name	Iplilimumab 3 mg/kg
Investigational medicinal product code	
Other name	Yervoy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was administered at a dose of 3 mg/kg body weight during the second 'boost' treatment in cohort 1, and in both the first and the second 'boost' treatment in cohort 2 together with nivolumab at 1 mg/kg. 'Boost' treatment was always administered for two cycles (Q2W).
Subsequent tumor assessment according to RECIST 1.1 informed the next treatment. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, eligible patients received a second 'boost' treatment. Patients with stable disease and ineligible for further boosts treatment were also switched to nivolumab maintenance treatment at 240 mg fixed dose. Patients with progressive disease and ineligible for further 'boost' treatment were decleared as immunotherapy resistant, and discontiued treatment within the study.

Arm title	Cohort 1, 2nd/3rd line

Arm description:

Patients who received 2nd or 3rd-line treatment under protocol version 3.0. Under this version, nivolumab was given at 3 mg/kg and ipilimumab at 1 mg/kg during the first boost treatment, and nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg during the second boost treatment.
Of the 44 patients in this cohort, 10 continued nivo mono maintenance after induction, 23 received a first boost treatment, and 11 discontinued treatment. Of the 23 patients who received a first boost treatment, 1 could switch to nivo maintenance, 16 continued with a second boost treatment, and 6 discontinued treatment. Of the 16 patients who received a second boost treatment, 6 could switch to nivo maintenance, 6 discontinued treatment due to adverse events, death or other reasons, and 4 were found immunotherapy resistant.

Arm type	Experimental
Investigational medicinal product name	Nivolumab 240 mg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a fixed dose of 240 mg IV for four cycles of induction treatment (Q2W). Subsequently, tumor assessment according to RECIST 1.1 was carried out. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, treatment was switched to a 'boost' treatment of combined nivolumab and

ipilimumab. If patients developed progressive disease at any time point during maintenance therapy, treatment was also switched to a 'boost' using combined nivolumab and ipilimumab.

Investigational medicinal product name	Nivolumab 3 mg/kg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a dose of 3 mg/kg body weight during the first 'boost' treatment in cohort 1 for two cycles (Q2W) together with ipilimumab at 1 mg/kg. Subsequently, tumor assessment according to RECIST 1.1 was carried out. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, patients received a second 'boost' treatment.

Investigational medicinal product name	Ipilimumab 1 mg/kg
Investigational medicinal product code	
Other name	Yervoy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was administered at a dose of 1 mg/kg body weight during the first 'boost' treatment in cohort 1 for two cycles (Q2W) together with nivolumab at 3 mg/kg. Subsequently, tumor assessment according to RECIST 1.1 was carried out. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, patients received a second 'boost' treatment.

Investigational medicinal product name	Nivolumab 1 mg/kg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a dose of 1 mg/kg body weight during the second 'boost' treatment in cohort 1, and in both the first and the second 'boost' treatment in cohort 2 together with ipilimumab at 3 mg/kg. 'Boost' treatment was to be administered for two cycles (Q2W).
Subsequent tumor assessment according to RECIST 1.1 informed the next treatment. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, eligible patients received a second 'boost' treatment. Patients with stable disease and ineligible for further boosts treatment were also switched to nivolumab maintenance treatment at 240 mg fixed dose. Patients with progressive disease and ineligible for further 'boost' treatment were decleared as immunotherapy resistant, and discontiued treatment within the study.

Investigational medicinal product name	Iplilimumab 3 mg/kg
Investigational medicinal product code	
Other name	Yervoy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was administered at a dose of 3 mg/kg body weight during the second 'boost' treatment in cohort 1, and in both the first and the second 'boost' treatment in cohort 2 together with nivolumab at 1 mg/kg. 'Boost' treatment was to be administered for two cycles (Q2W).
Subsequent tumor assessment according to RECIST 1.1 informed the next treatment. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, eligible patients received a second 'boost' treatment. Patients with stable disease and ineligible for further boosts treatment were also switched to nivolumab maintenance treatment at 240 mg fixed dose. Patients with progressive disease and ineligible for further 'boost' treatment were decleared as immunotherapy resistant, and discontiued treatment within the study.

Arm title	Cohort 2, 1st/2nd/3rd line

Arm description:

Patients who received treatment under protocol version 4.0 or later versions. Under this version, all boost treatments were dosed at nivolumab 1 mg/kg and ipilimumab at 3 mg/kg. Of the 83 patients in this cohort, 3 received the study regimen as 1st-line treatment, 78 as 2nd line, and 3 as 3rd line. Of

these 83 patients, 20 continued nivo mono maintenance after induction, 44 received a first boost treatment, and 19 discontinued treatment. Of the 44 patients who received a first boost treatment, 6 could switch to nivo maintenance, 14 continued with a second boost treatment, and 24 discontinued treatment. Of the 14 patients who received a second boost treatment, 4 could switch to nivo maintenance, 6 discontinued treatment, and 4 were found immunotherapy resistant.

Arm type	Experimental
Investigational medicinal product name	Nivolumab 240 mg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a fixed dose of 240 mg IV for four cycles of induction treatment (Q2W). Subsequently, tumor assessment according to RECIST 1.1 was carried out. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, treatment was switched to a 'boost' treatment of combined nivolumab and ipilimumab. If patients developed progressive disease at any time point during maintenance therapy, treatment was also switched to a 'boost' using combined nivolumab and ipilimumab.

Investigational medicinal product name	Nivolumab 1 mg/kg
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab was administered at a dose of 1 mg/kg body weight during the second 'boost' treatment in cohort 1, and in both the first and the second 'boost' treatment in cohort 2 together with ipilimumab at 3 mg/kg. 'Boost' treatment was to be administered for two cycles (Q2W).
Subsequent tumor assessment according to RECIST 1.1 informed the next treatment. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, eligible patients received a second 'boost' treatment. Patients with stable disease and ineligible for further boosts treatment were also switched to nivolumab maintenance treatment at 240 mg fixed dose. Patients with progressive disease and ineligible for further 'boost' treatment were decleared as immunotherapy resistant, and discontiued treatment within the study.

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Dosage and administration details:

Ipilimumab was administered at a dose of 3 mg/kg body weight during the second 'boost' treatment in cohort 1, and in both the first and the second 'boost' treatment in cohort 2 together with nivolumab at 1 mg/kg. 'Boost' treatment was to be administered for two cycles (Q2W).
Subsequent tumor assessment according to RECIST 1.1 informed the next treatment. In case of complete or partial remission, treatment at 240 mg Q2W was continued as maintenance treatment. In case of stable or progressive disease, eligible patients received a second 'boost' treatment. Patients with stable disease and ineligible for further boosts treatment were also switched to nivolumab maintenance treatment at 240 mg fixed dose. Patients with progressive disease and ineligible for further 'boost' treatment were decleared as immunotherapy resistant, and discontiued treatment within the study.

Number of subjects in period 1	Cohort 1, 1st line	Cohort 1, 2nd/3rd line	Cohort 2, 1st/2nd/3rd line
Started	42	44	83
Completed	42	44	83

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1, 1st line

Reporting group description:

Patients who received 1st-line treatment under protocol version 3.0. Under this version, nivolumab was given at 3 mg/kg and ipilimumab at 1 mg/kg during the first boost treatment, and nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg during the second boost treatment.
Of the 42 patients in this cohort, 14 continued nivo mono maintenance after induction, 17 received a first boost treatment, and 11 discontinued treatment. Of the 17 patients who received a first boost treatment, 6 could switch to nivo maintenance, 7 continued with a second boost treatment, and 4 discontinued treatment. Of the 7 patients who received a second boost treatment, 4 could switch to nivo maintenance, two discontinued treatment due to adverse events, and 1 was found immunotherapy resistant.

Reporting group title	Cohort 1, 2nd/3rd line

Reporting group description:

Patients who received 2nd or 3rd-line treatment under protocol version 3.0. Under this version, nivolumab was given at 3 mg/kg and ipilimumab at 1 mg/kg during the first boost treatment, and nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg during the second boost treatment.
Of the 44 patients in this cohort, 10 continued nivo mono maintenance after induction, 23 received a first boost treatment, and 11 discontinued treatment. Of the 23 patients who received a first boost treatment, 1 could switch to nivo maintenance, 16 continued with a second boost treatment, and 6 discontinued treatment. Of the 16 patients who received a second boost treatment, 6 could switch to nivo maintenance, 6 discontinued treatment due to adverse events, death or other reasons, and 4 were found immunotherapy resistant.

Reporting group title	Cohort 2, 1st/2nd/3rd line

Reporting group description:

Patients who received treatment under protocol version 4.0 or later versions. Under this version, all boost treatments were dosed at nivolumab 1 mg/kg and ipilimumab at 3 mg/kg. Of the 83 patients in this cohort, 3 received the study regimen as 1st-line treatment, 78 as 2nd line, and 3 as 3rd line. Of these 83 patients, 20 continued nivo mono maintenance after induction, 44 received a first boost treatment, and 19 discontinued treatment. Of the 44 patients who received a first boost treatment, 6 could switch to nivo maintenance, 14 continued with a second boost treatment, and 24 discontinued treatment. Of the 14 patients who received a second boost treatment, 4 could switch to nivo maintenance, 6 discontinued treatment, and 4 were found immunotherapy resistant.

Reporting group values	Cohort 1, 1st line	Cohort 1, 2nd/3rd line	Cohort 2, 1st/2nd/3rd line
Number of subjects	42	44	83
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	18	27
From 65-84 years	30	26	56
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	13	12	26
Male	29	32	57

Karnofsky performance status (screening) Units: Subjects			
70	7	4	3
80	8	8	15
90	9	13	23
100	18	19	42
not reported	0	0	0

Reporting group values	Total		
Number of subjects	169		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	57		
From 65-84 years	112		
85 years and over	0		
Gender categorical Units: Subjects			
Female	51		
Male	118		
Karnofsky performance status (screening) Units: Subjects			
70	14		
80	31		
90	45		
100	79		
not reported	0		

End points

End points reporting groups

Reporting group title	Cohort 1, 1st line

Reporting group description:

Patients who received 1st-line treatment under protocol version 3.0. Under this version, nivolumab was given at 3 mg/kg and ipilimumab at 1 mg/kg during the first boost treatment, and nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg during the second boost treatment.
Of the 42 patients in this cohort, 14 continued nivo mono maintenance after induction, 17 received a first boost treatment, and 11 discontinued treatment. Of the 17 patients who received a first boost treatment, 6 could switch to nivo maintenance, 7 continued with a second boost treatment, and 4 discontinued treatment. Of the 7 patients who received a second boost treatment, 4 could switch to nivo maintenance, two discontinued treatment due to adverse events, and 1 was found immunotherapy resistant.

Reporting group title	Cohort 1, 2nd/3rd line

Reporting group description:

Patients who received 2nd or 3rd-line treatment under protocol version 3.0. Under this version, nivolumab was given at 3 mg/kg and ipilimumab at 1 mg/kg during the first boost treatment, and nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg during the second boost treatment.
Of the 44 patients in this cohort, 10 continued nivo mono maintenance after induction, 23 received a first boost treatment, and 11 discontinued treatment. Of the 23 patients who received a first boost treatment, 1 could switch to nivo maintenance, 16 continued with a second boost treatment, and 6 discontinued treatment. Of the 16 patients who received a second boost treatment, 6 could switch to nivo maintenance, 6 discontinued treatment due to adverse events, death or other reasons, and 4 were found immunotherapy resistant.

Reporting group title	Cohort 2, 1st/2nd/3rd line

Reporting group description:

Patients who received treatment under protocol version 4.0 or later versions. Under this version, all boost treatments were dosed at nivolumab 1 mg/kg and ipilimumab at 3 mg/kg. Of the 83 patients in this cohort, 3 received the study regimen as 1st-line treatment, 78 as 2nd line, and 3 as 3rd line. Of these 83 patients, 20 continued nivo mono maintenance after induction, 44 received a first boost treatment, and 19 discontinued treatment. Of the 44 patients who received a first boost treatment, 6 could switch to nivo maintenance, 14 continued with a second boost treatment, and 24 discontinued treatment. Of the 14 patients who received a second boost treatment, 4 could switch to nivo maintenance, 6 discontinued treatment, and 4 were found immunotherapy resistant.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the number of subjects with a best overall response 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.

End point type	Primary

End point timeframe:

Objective response observed between 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.

End point values	Cohort 1, 1st line	Cohort 1, 2nd/3rd line	Cohort 2, 1st/2nd/3rd line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	44	83	
Units: Subjects with objective response				
ORR	20	12	27	
CR	3	3	9	
PR	17	9	18	
SD	4	8	8	
PD	10	15	35	
Death	8	8	11	
NE	0	1	2	

Statistical analyses

Statistical analysis title	Clopper-Pearson anaylisis of ORR

Statistical analysis description:

For cohort 1 - 1st line, ORR was significantly better than pre-specified: Clopper-Pearson (exact) 90%CI 0.34–0.61 (p<0.001, one-sided).
For cohort 1 - 2nd/3rd line, ORR was 27% (n=12; Clopper-Pearson [exact] 90%CI 0.17–0.40 (p=0.15, one-sided).
For cohort 2 - 1st/2nd/3rd line, ORR again was significantly better than pre-specified: Clopper-Pearson (exact) 90%CI 0.24–0.42 (p=0.005, one-sided).

Comparison groups	Cohort 1, 1st line v Cohort 2, 1st/2nd/3rd line v Cohort 1, 2nd/3rd line
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [1]
Method	Clopper-Pearson

Notes:

[1] - Please refer to Analysis Description for results of individual statistical analysis of all treatment cohorts

Secondary: Time to first response (TTR)

End point title	Time to first response (TTR)

End point description:

Medians that were not reached during the study's observation period, or confidence limits that were not estimable are represented as '10000000'.

End point type	Secondary

End point timeframe:

TTR was defined as the time from first dosing date to the date of the first confirmed response thereafter.

End point values	Cohort 1, 1st line	Cohort 1, 2nd/3rd line	Cohort 2, 1st/2nd/3rd line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	44	83	
Units: Months				
median (confidence interval 95%)	3.3 (2.5 to 10000000)	10000000 (4.5 to 10000000)	19.5 (4.8 to 10000000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Confidence limits that were not estimable are represented as '10000000'.

End point type	Secondary

End point timeframe:

DOR was defined as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occured first.

End point values	Cohort 1, 1st line	Cohort 1, 2nd/3rd line	Cohort 2, 1st/2nd/3rd line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	44	83	
Units: Months				
median (confidence interval 95%)	9.1 (4.1 to 10000000)	18.7 (4.2 to 40.0)	18.0 (6.9 to 34.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

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	Cohort 1, 1st line	Cohort 1, 2nd/3rd line	Cohort 2, 1st/2nd/3rd line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	44	83	
Units: Months				
median (confidence interval 95%)	3.0 (1.8 to 6.8)	1.9 (1.7 to 5.8)	1.9 (1.8 to 3.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

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 had not died was censored at last known date alive.

End point values	Cohort 1, 1st line	Cohort 1, 2nd/3rd line	Cohort 2, 1st/2nd/3rd line	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	44	83	
Units: Months				
median (confidence interval 95%)	16.4 (7.3 to 28.5)	8.3 (5.3 to 19.3)	7.6 (5.0 to 14.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE were to be collected that occur from first IMP administration until 100 days of IMP discontinuation. Moreover, investigators were to report any SAE occuring after these time periods believed to be related to IMP or protocol-specified procedures.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	x

Reporting groups

Reporting group title	CSP V3
Reporting group description: -	
Reporting group title	CSP V4f

Reporting group description: -

Serious adverse events	CSP V3	CSP V4f	
Total subjects affected by serious adverse events			
subjects affected / exposed	77 / 86 (89.53%)	71 / 83 (85.54%)	
number of deaths (all causes)	60	53	
number of deaths resulting from adverse events	38	42	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			

subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor pain			
subjects affected / exposed	1 / 86 (1.16%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumor associated fever			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	24 / 86 (27.91%)	34 / 83 (40.96%)	
occurrences causally related to treatment / all	0 / 26	0 / 36	
deaths causally related to treatment / all	0 / 22	0 / 31	
Metastases to spinal cord			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 86 (0.00%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Elective surgery			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin neoplasm excision			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
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			
Chest pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 86 (4.65%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Impaired healing			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mucosal inflammation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 86 (4.65%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 86 (1.16%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia aspiration			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	4 / 86 (4.65%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 86 (2.33%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated pneumonitis			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical condition decreased			
subjects affected / exposed	1 / 86 (1.16%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric anastomosis complication			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract stoma complication			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiovascular disorder			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Epilepsy			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Somnolence			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune neuropathy			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 86 (2.33%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	2 / 86 (2.33%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diplopia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 86 (3.49%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Constipation			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 86 (4.65%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	2 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula of small intestine			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	10 / 86 (11.63%)	13 / 83 (15.66%)	
occurrences causally related to treatment / all	10 / 11	16 / 17	
deaths causally related to treatment / all	1 / 1	1 / 1	
Obstructive pancreatitis			

subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	3 / 86 (3.49%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (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			
Dermatitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash papular			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			

subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis haemorrhagic			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 86 (3.49%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	5 / 86 (5.81%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	3 / 86 (3.49%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric compression			

subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthalgia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myalgia			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	2 / 86 (2.33%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 86 (1.16%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 86 (3.49%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 2	
Urethral abscess			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	14 / 86 (16.28%)	8 / 83 (9.64%)	
occurrences causally related to treatment / all	0 / 17	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 86 (2.33%)	3 / 83 (3.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 86 (0.00%)	2 / 83 (2.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Staphylococcal sepsis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis bacterial			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			

subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infected fistula			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 86 (1.16%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 83 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	1 / 86 (1.16%)	0 / 83 (0.00%)	
occurrences causally related to treatment / all	0 / 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	CSP V3	CSP V4f	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 86 (91.86%)	80 / 83 (96.39%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 86 (6.98%)	3 / 83 (3.61%)	
occurrences (all)	6	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 86 (32.56%)	33 / 83 (39.76%)	
occurrences (all)	33	36	
Oedema peripheral			
subjects affected / exposed	9 / 86 (10.47%)	5 / 83 (6.02%)	
occurrences (all)	9	5	
Pain			
subjects affected / exposed	3 / 86 (3.49%)	8 / 83 (9.64%)	
occurrences (all)	3	8	
Pyrexia			
subjects affected / exposed	16 / 86 (18.60%)	10 / 83 (12.05%)	
occurrences (all)	20	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 86 (17.44%)	6 / 83 (7.23%)	
occurrences (all)	15	6	
Dyspnoea			
subjects affected / exposed	13 / 86 (15.12%)	9 / 83 (10.84%)	
occurrences (all)	17	10	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	7 / 86 (8.14%)	2 / 83 (2.41%)	
occurrences (all)	10	2	
Sleep disorder			
subjects affected / exposed	6 / 86 (6.98%)	11 / 83 (13.25%)	
occurrences (all)	6	11	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 86 (3.49%)	6 / 83 (7.23%)	
occurrences (all)	5	6	
Amylase increased			
subjects affected / exposed	4 / 86 (4.65%)	4 / 83 (4.82%)	
occurrences (all)	4	6	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 86 (3.49%)	7 / 83 (8.43%)	
occurrences (all)	3	8	
Blood creatinine increased			
subjects affected / exposed	8 / 86 (9.30%)	5 / 83 (6.02%)	
occurrences (all)	11	6	
C-reactive protein increased			
subjects affected / exposed	3 / 86 (3.49%)	5 / 83 (6.02%)	
occurrences (all)	3	5	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 86 (0.00%)	5 / 83 (6.02%)	
occurrences (all)	0	7	
Lipase increased			
subjects affected / exposed	8 / 86 (9.30%)	3 / 83 (3.61%)	
occurrences (all)	10	6	
Weight decreased			
subjects affected / exposed	2 / 86 (2.33%)	7 / 83 (8.43%)	
occurrences (all)	2	7	
Hepatic enzyme increased			
subjects affected / exposed	6 / 86 (6.98%)	4 / 83 (4.82%)	
occurrences (all)	10	4	
Hyperkalaemia			

subjects affected / exposed	2 / 86 (2.33%)	5 / 83 (6.02%)	
occurrences (all)	5	5	
Hypokalaemia			
subjects affected / exposed	2 / 86 (2.33%)	7 / 83 (8.43%)	
occurrences (all)	2	9	
Decreased appetite			
subjects affected / exposed	14 / 86 (16.28%)	9 / 83 (10.84%)	
occurrences (all)	16	10	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 86 (4.65%)	10 / 83 (12.05%)	
occurrences (all)	4	13	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 86 (13.95%)	10 / 83 (12.05%)	
occurrences (all)	13	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 86 (6.98%)	5 / 83 (6.02%)	
occurrences (all)	6	5	
Abdominal pain upper			
subjects affected / exposed	6 / 86 (6.98%)	7 / 83 (8.43%)	
occurrences (all)	9	8	
Constipation			
subjects affected / exposed	10 / 86 (11.63%)	13 / 83 (15.66%)	
occurrences (all)	12	13	
Diarrhoea			
subjects affected / exposed	20 / 86 (23.26%)	20 / 83 (24.10%)	
occurrences (all)	38	32	
Nausea			
subjects affected / exposed	18 / 86 (20.93%)	13 / 83 (15.66%)	
occurrences (all)	18	15	
Vomiting			
subjects affected / exposed	10 / 86 (11.63%)	7 / 83 (8.43%)	
occurrences (all)	13	13	
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	6 / 86 (6.98%)	3 / 83 (3.61%)	
occurrences (all)	6	5	
Erythema			
subjects affected / exposed	7 / 86 (8.14%)	4 / 83 (4.82%)	
occurrences (all)	7	4	
Hyperhidrosis			
subjects affected / exposed	7 / 86 (8.14%)	1 / 83 (1.20%)	
occurrences (all)	7	1	
Pruritus			
subjects affected / exposed	12 / 86 (13.95%)	13 / 83 (15.66%)	
occurrences (all)	16	18	
Rash			
subjects affected / exposed	19 / 86 (22.09%)	21 / 83 (25.30%)	
occurrences (all)	32	25	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 86 (5.81%)	3 / 83 (3.61%)	
occurrences (all)	6	3	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	7 / 86 (8.14%)	8 / 83 (9.64%)	
occurrences (all)	7	8	
Hypothyroidism			
subjects affected / exposed	11 / 86 (12.79%)	11 / 83 (13.25%)	
occurrences (all)	11	15	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 86 (11.63%)	5 / 83 (6.02%)	
occurrences (all)	14	6	
Back pain			
subjects affected / exposed	9 / 86 (10.47%)	13 / 83 (15.66%)	
occurrences (all)	10	14	
Bone pain			
subjects affected / exposed	3 / 86 (3.49%)	5 / 83 (6.02%)	
occurrences (all)	4	5	

Flank pain			
subjects affected / exposed	5 / 86 (5.81%)	5 / 83 (6.02%)	
occurrences (all)	6	5	
Muscular weakness			
subjects affected / exposed	5 / 86 (5.81%)	3 / 83 (3.61%)	
occurrences (all)	7	3	
Musculoskeletal pain			
subjects affected / exposed	7 / 86 (8.14%)	5 / 83 (6.02%)	
occurrences (all)	7	5	
Myalgia			
subjects affected / exposed	4 / 86 (4.65%)	5 / 83 (6.02%)	
occurrences (all)	5	5	
Pain in extremity			
subjects affected / exposed	6 / 86 (6.98%)	9 / 83 (10.84%)	
occurrences (all)	7	15	
Infections and infestations			
Infection			
subjects affected / exposed	5 / 86 (5.81%)	2 / 83 (2.41%)	
occurrences (all)	5	2	
Nasopharyngitis			
subjects affected / exposed	14 / 86 (16.28%)	7 / 83 (8.43%)	
occurrences (all)	19	11	
Rhinitis			
subjects affected / exposed	6 / 86 (6.98%)	1 / 83 (1.20%)	
occurrences (all)	7	1	
Urinary tract infection			
subjects affected / exposed	17 / 86 (19.77%)	13 / 83 (15.66%)	
occurrences (all)	38	18	
Corona virus infection			
subjects affected / exposed	1 / 86 (1.16%)	6 / 83 (7.23%)	
occurrences (all)	1	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2019	In the initial version of the protocol, the two nivolumab/ipilimumab boost cycles used different dosing of the two IMPs: for the first boost (boost cycles 1 and 2), nivolumab was to be given at 3 mg/kg and ipilimumab at 1 mg/kg, while dosing was nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg for the second boost (boost cycles 3 and 4). Following the publication of results of the Checkmate 032 study, the protocol was amended to change dosing for the first boost (cycles 1 and 2) to nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg, thus applying the same dosing in all boost cycles, since this dosing pattern had shown better efficacy and only slightly higher toxicity in the Checkmate 032 study. Furthermore, the recruitment target was reduced from initially 250 participants to 225, and the recruitment period was extended.
07 April 2020	Following a recruitment stop for 1st-line patients due to safety concerns, an interim analysis, and feedback from the competent authority, recruitment of 1st-line patients was terminated and the termination implemented with this amendment. Target enrollment was updated to 190 participants, and the planned statistical analysis was adapted accordingly, implementing a statistical power of 85%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 January 2019	Recruitment of 1st-line participants was paused by the sponsor as a results of the scheduled activities of the study's data monitoring committee (DMC). Upon a routine analysis that was based on 39 study participants, the DMC observed an unexpected accumulation of SAEs with fatal outcomes in the 1st-line cohort that occured within 8 weeks of study inclusion. After the recruitment halt for 1st-line patients, an unplanned safety interim analysis was conducted that was based on 88 study participants. The DMC concluded that there were no unexpected safety risks and expressed no reservations about resuming the inclusion of first-line patients into the study. However, the sponsor'S request to reopen the study to 1st-line participants was denied by the competent authority, and recruitment of 1st-line patients therefore terminated and implemented by protocol amendment.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36868252

http://www.ncbi.nlm.nih.gov/pubmed/38722641

http://www.ncbi.nlm.nih.gov/pubmed/35275706