



Clinical trial results:

A phase II trial of nivolumab in combination with ipilimumab to evaluate efficacy and safety in relapsed lung cancer and to evaluate biomarkers predictive for response to immune checkpoint inhibition

Summary

EudraCT number	2016-003334-25
Trial protocol	DE
Global end of trial date	20 November 2023

Results information

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

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-2785
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03083691
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Inken Terjung, University of Cologne, +49 22147898766, inken.terjung@uk-koeln.de
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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	20 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2022
Global end of trial reached?	Yes
Global end of trial date	20 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cohort 1:

To assess ORR when ipilimumab is added to nivolumab after progression on nivolumab monotherapy in patients relapsed with non-squamous NSCLC (second line).

Note: Cohort 1 was closed for enrollment. Subjects who started screening for cohort 1 prior to stop of recruitment initiated by Coordinating PI on April 25 2019 continue to receive treatment. SCLC subjects eligible for BIOLUMA are enrolled in cohort 2b after TMB-Prescreening from October 29 2018 on.

Cohort 2a:

To assess ORR of the combination therapy of ipilimumab and nivolumab in patients with relapsed SCLC and non-discriminated TMB (second line).

Note: Cohort 2a was closed for enrollment. SCLC Subjects eligible for BIOLUMA are enrolled in Cohort 2b after TMB-Prescreening from October 29 2018 on.

Cohort 2b:

To assess ORR of the combination therapy of ipilimumab and nivolumab in patients with relapsed SCLC and high TMB (second line).

Protection of trial subjects:

The trial data including study procedures, safety results and efficacy results were extensively reviewed by the participating DMSC members on a regular basis.

In the initial cohort 2 (SCLC, not TMB-discriminated), two treatment-related deaths occurred. One patient died from pneumonitis, one patient experienced a fatal course of encephalitis. Both patients did have a good tumor response within the trial. As during that time new data were presented, which indicated that the combination therapy of nivolumab and ipilimumab in SCLC patients only has beneficial effects in patients with high tumor mutation burden (23), a risk-benefit consideration lead to stop of recruitment in cohort 2. The remaining SCLC patients in the trial were treated analogous to the NSCLC patients in cohort 1.

The cohort was re-opened for patients with high tumor mutation burden only (cohort 2b) and the former cohort 2 was renamed to cohort 2a for clarification reasons.

In cohort 2b, one patient died due to study-procedure related complications: in order to gain a tumor biopsy, a bronchoscopy had been performed. During the procedure, the patient died from a cardiogenic shock. The patient had achieved a partial response to the study treatment. As a consequence of that fatal event, the protocol was amended (protocol amendment no.4) for cohort 2b to change tumor biopsy before study treatment from mandatory to optional.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 April 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	Germany: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	47
From 65 to 84 years	42
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment cohort 1: 05/04/2017 - 25/04/2019

Recruitment cohort 2a: 05/04/2017 - 15/12/2017

Recruitment cohort 2b: 24/10/2018 - 28/07/2022

Last Patient Out: 20/11/2023

Pre-assignment

Screening details:

Screenings: 127 patients

Screening failures: 37 patients (cohort 1: 20; cohort 2a: 10; cohort 2b: 7)

Reasons for screening failures:

- non-fulfillment of inclusion criterion: 17 patients
- fulfillment of exclusion criterion: 18 patients
- withdrawal of ICF during screening: 2 patients

Pre-screenings (for cohort 2b only): 297 patients

Period 1

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

Blinding implementation details:

As this was a single-arm, non-randomized open-label study, blinding did not apply.

Arms

Arm title	Single arm
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Arm description:

Cohort 1 (non-squamous NSCLC):

Treatment Part A: nivolumab 240 mg IV q2w as monotherapy; at the time of disease progression another re-biopsy; then Treatment Part B: combination therapy (nivolumab in a dose of 3 mg/kg q2w together with ipilimumab 1 mg/kg IV q6w (with a 12 days gap between last dose of nivolumab and nivolumab + ipilimumab).

In case of occurrence of intolerable toxicity attributed to the combination therapy, treatment was continued with nivolumab 240 mg q2w monotherapy only.

Cohort 2a (SCLC all-comer) + 2b (SCLC TMB high):

Treatment Part A: nivolumab 1 mg/kg q3w together with ipilimumab 3 mg/kg q3w for a total of four doses, in case of occurrence of an AE and if AE was attributed to combination therapy, it was possible to continue treatment with Part B without completion of the four combined doses.

Treatment Part B: another optional rebiopsy, then nivolumab 240 mg q2w monotherapy until disease progression or unacceptable toxicity

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

Dosage and administration details:

Cohort 1:

- Part A: nivolumab (monotherapy) 240 mg as a 30 minute IV-infusion, every 2 weeks
- Part B: nivolumab (in combination with ipilimumab) dose = 3 mg/kg as a 30 minute IV-infusion, every 2 weeks

Cohort 2a and 2b:

- Part A: 4 doses of nivolumab (in combination with ipilimumab), dose = 1 mg/kg as a 30 minute IV-infusion, every 3 weeks
- Part B: nivolumab (monotherapy) 240 mg as a 30 minute IV-infusion every 2 weeks

For combination therapy with ipilimumab: Nivolumab should be administered as a 30 minute infusion, followed by Ipilimumab as a 90 minutes infusion (in between 30 min break)

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

Dosage and administration details:

Cohort 1:

- Part A: no administration of ipilimumab
- Part B: ipilimumab (in combination with nivolumab) dose = 1 mg/kg as a 90 minute IV-infusion, every 6 weeks

Cohort 2a and 2b:

- Part A: four doses of ipilimumab (in combination with nivolumab) dose = 3 mg/kg as a 90 minute IV-infusion, every 3 weeks
- Part B: no administration of ipilimumab

For combination therapy of nivolumab + ipilimumab: nivolumab should be administered as a 30 minute infusion, followed by ipilimumab as a 90 minute infusion (in between 30 min break)

Number of subjects in period 1	Single arm
Started	90
Completed	90

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	90	90	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	47	47	
From 65-84 years	42	42	
85 years and over	1	1	
Age continuous			
Units: years			
median	63.0		
full range (min-max)	38 to 85	-	
Gender categorical			
Units: Subjects			
Female	41	41	
Male	49	49	

Subject analysis sets

Subject analysis set title	Response-evaluable population - cohort 1
Subject analysis set type	Per protocol

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) and patients who received additional tumor treatment within the trial). The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.

Subject analysis set title	Response-evaluable population - cohort 2b
Subject analysis set type	Per protocol

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts)). The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.

Subject analysis set title	Response-evaluable population - cohort 2a
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Subject analysis set type	Per protocol
Subject analysis set description:	
<p>The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) patients in cohort 2a treated analogously to cohort 1).</p> <p>The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event. Subjects in cohort 2a, who were treated analogous to cohort 1 for safety reasons after two treatment-related deaths occurred, were only included in the response-evaluable population, if they received at least one dose of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg + follow-up assessment before switch.</p>	
Subject analysis set title	Safety analysis population - cohort 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
<p>The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.</p>	
Subject analysis set title	Safety analysis population - cohort 2b
Subject analysis set type	Per protocol
Subject analysis set description:	
<p>The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.</p>	
Subject analysis set title	Safety analysis population - cohort 2a
Subject analysis set type	Per protocol
Subject analysis set description:	
<p>The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.</p>	

Reporting group values	Response-evaluable population - cohort 1	Response-evaluable population - cohort 2b	Response-evaluable population - cohort 2a
Number of subjects	25	45	15
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	26	7
From 65-84 years	13	19	8
85 years and over	0	0	0
Age continuous Units: years			
median	66.0	62.0	65.0
full range (min-max)	42 to 79	38 to 79	46 to 80
Gender categorical Units: Subjects			
Female	12	23	5
Male	13	22	10

Reporting group values	Safety analysis population - cohort 1	Safety analysis population - cohort 2b	Safety analysis population - cohort 2a
Number of subjects	27	45	18
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)	13	26	8
From 65-84 years	13	19	10
85 years and over	1	0	0
Age continuous Units: years			
median	66.0	62.0	65.5
full range (min-max)	42 to 85	38 to 79	64 to 80
Gender categorical Units: Subjects			
Female	12	23	6
Male	15	22	12

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description:	
Cohort 1 (non-squamous NSCLC): Treatment Part A: nivolumab 240 mg IV q2w as monotherapy; at the time of disease progression another re-biopsy; then Treatment Part B: combination therapy (nivolumab in a dose of 3 mg/kg q2w together with ipilimumab 1 mg/kg IV q6w (with a 12 days gap between last dose of nivolumab and nivolumab + ipilimumab)). In case of occurrence of intolerable toxicity attributed to the combination therapy, treatment was continued with nivolumab 240 mg q2w monotherapy only.	
Cohort 2a (SCLC all-comer) + 2b (SCLC TMB high): Treatment Part A: nivolumab 1 mg/kg q3w together with ipilimumab 3 mg/kg q3w for a total of four doses, in case of occurrence of an AE and if AE was attributed to combination therapy, it was possible to continue treatment with Part B without completion of the four combined doses. Treatment Part B: another optional rebiopsy, then nivolumab 240 mg q2w monotherapy until disease progression or unacceptable toxicity	
Subject analysis set title	Response-evaluable population - cohort 1
Subject analysis set type	Per protocol
Subject analysis set description:	
The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) and patients who received additional tumor treatment within the trial). The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.	
Subject analysis set title	Response-evaluable population - cohort 2b
Subject analysis set type	Per protocol
Subject analysis set description:	
The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts)). The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.	
Subject analysis set title	Response-evaluable population - cohort 2a
Subject analysis set type	Per protocol
Subject analysis set description:	
The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) patients in cohort 2a treated analogously to cohort 1). The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event. Subjects in cohort 2a, who were treated analogous to cohort 1 for safety reasons after two treatment-related deaths occurred, were only included in the response-evaluable population, if they received at least one dose of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg + follow-up assessment before switch.	
Subject analysis set title	Safety analysis population - cohort 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.	
Subject analysis set title	Safety analysis population - cohort 2b
Subject analysis set type	Per protocol

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

Subject analysis set title	Safety analysis population - cohort 2a
Subject analysis set type	Per protocol

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

Primary: Overall response rate (ORR)

End point title	Overall response rate (ORR)
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End point description:

ORR per RECIST 1.1 with 95% confidence interval was calculated based on all patients in the response-evaluable population. ORR was defined as proportion of subjects whose best confirmed objective response is a CR or PR as assessed by RECIS v1.1, relative to the evaluable population.

Cohort 1:

ORR according to investigator-assessed RECIST 1.1 criteria of the combination of nivolumab and ipilimumab after progression on nivolumab monotherapy in patients re-lapsed with non-squamous NSCLC.

Cohort 2a:

ORR according to investigator-assessed RECIST 1.1 criteria of the combination of nivolumab and ipilimumab in patients with relapsed SCLC and non-discriminated TMB.

Cohort 2b:

ORR according to investigator-assessed RECIST 1.1 criteria of the combination of nivolumab and ipilimumab in patients with relapsed SCLC and high TMB.

End point type	Primary
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End point timeframe:

05/04/2017 to 31/08/2022

End point values	Response-evaluable population - cohort 1	Response-evaluable population - cohort 2b	Response-evaluable population - cohort 2a	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12 ^[1]	43 ^[2]	15	
Units: patients	1	4	4	

Notes:

[1] - Only 12 patients were treated in treatment part B. ORR of treatment part B is the primary endpoint

[2] - 2 pts are not included in per protocol analysis due to add. tumor treatment or staging too early

Statistical analyses

Statistical analysis title	Cohort 1, Cohort 2a, Cohort 2b
Comparison groups	Response-evaluable population - cohort 2b v Response-evaluable population - cohort 1 v Response-evaluable population - cohort 2a

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 ^[3]
Method	p not applicable

Notes:

[3] - No comparison was performed between the 3 cohorts

Statistical analysis title	Cohort 1, Cohort 2a, Cohort 2b
Comparison groups	Response-evaluable population - cohort 2a v Response-evaluable population - cohort 1 v Response-evaluable population - cohort 2b
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 ^[4]
Method	p not applicable

Notes:

[4] - No comparison between the 3 cohorts was performed

Statistical analysis title	Cohort 1, Cohort 2a, Cohort 2b
Comparison groups	Response-evaluable population - cohort 2b v Response-evaluable population - cohort 2a v Response-evaluable population - cohort 1
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 ^[5]
Method	p not applicable

Notes:

[5] - No comparison was done between the 3 cohorts

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first intake of study drug (or if adverse events related to study procedures, after signature of informed consent), and for a minimum of 100 days following the last intake of study drug (or for serious adverse events until end of survival follow-up)

Adverse event reporting additional description:

Frequent study visits with laboratory assessments.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

NSCLC

Reporting group title	Cohort 2a
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Reporting group description:

SCLC all-comer

Reporting group title	Cohort 2b
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Reporting group description:

SCLC TMB high

Serious adverse events	Cohort 1	Cohort 2a	Cohort 2b
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)	18 / 18 (100.00%)	43 / 45 (95.56%)
number of deaths (all causes)	18	16	37
number of deaths resulting from adverse events	18	16	37
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	14 / 27 (51.85%)	9 / 18 (50.00%)	25 / 45 (55.56%)
occurrences causally related to treatment / all	0 / 15	0 / 10	0 / 28
deaths causally related to treatment / all	0 / 14	0 / 9	0 / 27
Metastases to meninges			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Small cell lung cancer			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pseudoprogression			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheterisation venous			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 27 (7.41%)	1 / 18 (5.56%)	5 / 45 (11.11%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 5
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)	0 / 18 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 27 (3.70%)	2 / 18 (11.11%)	3 / 45 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Injection site inflammation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 27 (14.81%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	2 / 5	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Dyspnoea			

subjects affected / exposed	4 / 27 (14.81%)	2 / 18 (11.11%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 27 (7.41%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 18 (11.11%)	3 / 45 (6.67%)
occurrences causally related to treatment / all	0 / 0	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood bilirubin increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lipase increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic enzymes increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur fracture			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			

Aphasia	subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
	occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident	subjects affected / exposed	2 / 27 (7.41%)	0 / 18 (0.00%)	0 / 45 (0.00%)
	occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diabetic hyperosmolar coma	subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
	occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation	subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy	subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis	subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial	subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis	subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy	subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	0 / 45 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory loss			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune pancreatitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 27 (7.41%)	1 / 18 (5.56%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	2 / 3	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			

subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated pancreatitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 27 (7.41%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 27 (7.41%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelocaliectasis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	1 / 27 (3.70%)	2 / 18 (11.11%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hyperthyroidism			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 18 (11.11%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia necrotising			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 18 (0.00%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 27 (7.41%)	0 / 18 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	0 / 45 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 27 (0.00%)	1 / 18 (5.56%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 27 (3.70%)	3 / 18 (16.67%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1	Cohort 2a	Cohort 2b
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)	16 / 18 (88.89%)	39 / 45 (86.67%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	1 / 18 (5.56%)	6 / 45 (13.33%)
occurrences (all)	1	4	15
Amylase increased			
subjects affected / exposed	1 / 27 (3.70%)	3 / 18 (16.67%)	6 / 45 (13.33%)
occurrences (all)	3	3	8
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	3 / 18 (16.67%)	5 / 45 (11.11%)
occurrences (all)	1	5	11
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 27 (3.70%)	1 / 18 (5.56%)	7 / 45 (15.56%)
occurrences (all)	2	1	8
Blood creatinine increased			
subjects affected / exposed	1 / 27 (3.70%)	4 / 18 (22.22%)	3 / 45 (6.67%)
occurrences (all)	1	6	3
C-reactive protein increased			
subjects affected / exposed	3 / 27 (11.11%)	2 / 18 (11.11%)	1 / 45 (2.22%)
occurrences (all)	3	2	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 27 (3.70%)	2 / 18 (11.11%)	6 / 45 (13.33%)
occurrences (all)	13	3	14
Lipase increased			
subjects affected / exposed	1 / 27 (3.70%)	3 / 18 (16.67%)	9 / 45 (20.00%)
occurrences (all)	4	5	16
Lymphocyte count decreased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 18 (0.00%)	9 / 45 (20.00%)
occurrences (all)	0	0	18
Platelet count decreased			

subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	2 / 18 (11.11%) 2	4 / 45 (8.89%) 5
Weight decreased subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 18 (0.00%) 0	4 / 45 (8.89%) 4
Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 11	2 / 18 (11.11%) 2	2 / 45 (4.44%) 2
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	7 / 27 (25.93%) 10	3 / 18 (16.67%) 4	5 / 45 (11.11%) 7
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 18 (0.00%) 0	5 / 45 (11.11%) 5
Chest pain subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 6	1 / 18 (5.56%) 1	0 / 45 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 8	9 / 18 (50.00%) 10	17 / 45 (37.78%) 18
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 18 (5.56%) 1	5 / 45 (11.11%) 6
Pyrexia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4	3 / 18 (16.67%) 3	0 / 45 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	0 / 18 (0.00%) 0	4 / 45 (8.89%) 5
Diarrhoea subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 7	8 / 18 (44.44%) 13	15 / 45 (33.33%) 21

Nausea subjects affected / exposed occurrences (all)	9 / 27 (33.33%) 10	5 / 18 (27.78%) 6	9 / 45 (20.00%) 9
Vomiting subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 18 (5.56%) 1	3 / 45 (6.67%) 4
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	9 / 27 (33.33%) 11	4 / 18 (22.22%) 4	4 / 45 (8.89%) 6
Dyspnoea subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3	2 / 18 (11.11%) 2	3 / 45 (6.67%) 5
Pneumonitis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	3 / 18 (16.67%) 4	4 / 45 (8.89%) 4
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 18 (5.56%) 1	4 / 45 (8.89%) 4
Pruritus subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4	4 / 18 (22.22%) 4	13 / 45 (28.89%) 18
Rash subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 2	3 / 18 (16.67%) 3	8 / 45 (17.78%) 12
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	3 / 18 (16.67%) 3	3 / 45 (6.67%) 3
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	4 / 18 (22.22%) 4	4 / 45 (8.89%) 4
Hypothyroidism			

subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	2 / 18 (11.11%) 2	1 / 45 (2.22%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 27 (7.41%)	5 / 18 (27.78%)	3 / 45 (6.67%)
occurrences (all)	2	6	6
Back pain			
subjects affected / exposed	2 / 27 (7.41%)	2 / 18 (11.11%)	4 / 45 (8.89%)
occurrences (all)	5	4	4
Infections and infestations			
Infection			
subjects affected / exposed	3 / 27 (11.11%)	1 / 18 (5.56%)	3 / 45 (6.67%)
occurrences (all)	6	1	4
Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 18 (5.56%)	3 / 45 (6.67%)
occurrences (all)	1	1	3
Urinary tract infection			
subjects affected / exposed	3 / 27 (11.11%)	4 / 18 (22.22%)	3 / 45 (6.67%)
occurrences (all)	5	4	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 27 (14.81%)	0 / 18 (0.00%)	7 / 45 (15.56%)
occurrences (all)	5	0	8
Hypokalaemia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 18 (11.11%)	5 / 45 (11.11%)
occurrences (all)	1	4	5
Hyponatraemia			
subjects affected / exposed	3 / 27 (11.11%)	2 / 18 (11.11%)	10 / 45 (22.22%)
occurrences (all)	3	3	13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 January 2018	Protocol Amendment 1 comprised replacement of deep rectal swabs by stool samples for microbiome analysis, as this sample modality was more feasible for patients to perform and a higher return flow for samples was expected. Some clarifications of reporting period for SAEs related to study drug or to study-related procedures were included as well as specification of SAE reporting of SAEs related to disease progression. Other changes in amendment 1 concerned new safety data on nivolumab and ipilimumab.
30 October 2018	With Protocol Amendment 2, cohort 2 was modified to include SCLC patients with high tumor mutation burden only and TMB pre-screening was implemented for SCLC patients. This amendment was necessary as in December 2017, two treatment-related deaths had occurred. As new data were presented, which indicated that the combination therapy of nivolumab and ipilimumab in SCLC patients only had beneficial effects in patients with high tumor mutation burden, a risk-benefit consideration led to stop of recruitment in cohort 2. The remaining SCLC patients in the trial were treated analogous to the NSCLC patients in cohort 1 for safety reasons.
18 December 2019	<p>Protocol Amendment 4: The original cohort 2 was subdivided in cohort 2a for the terminated cohort of SCLC patients who were not TMB discriminated and in cohort 2b for patients with high tumor mutation burden. The renaming was performed in order to have a clear separation of the biologically different patient groups. Additionally, the initial mandatory rebiopsy before study treatment was changed to optional in cohort 2b. This decision was made after one procedure-related death had occurred for bronchoscopic tumor biopsy in a trial subject who had responded well to study drug treatment.</p> <p>Protocol amendment 3 was rejected by EC, but approved by CA. Recruitment for NSCLC patients (cohort 1) was closed. This decision had been made as a high dropout rate from treatment part A to part B was observed. Thus, due to lack of feasibility, enrolment to this cohort was terminated early. Subjects enrolled into this cohort prior to the amendment continued to receive treatment with study drugs per protocol.</p> <p>For the SCLC cohort, the amendment included expansion of the patient number to a total of 79 trial subjects (TMB high plus TMB non-discriminated SCLC patients).</p>
05 June 2020	Protocol Amendment 5 comprised a modification of inclusion criteria for SCLC patients in cohort 2b. Given the fact, that some patients receive rechallenge treatment with a platinum-based therapy instead of topotecan, enrolment after 2nd line therapy was allowed independent of the drug used in 2nd line (with exception to monotherapy with anti-PD-1/-PD-L1/-CTLA-4 antibodies) to allow a more realistic treatment setting. Additionally, the interval between radiation of brain metastases and start of study treatment was eliminated as data indicated that both can be performed simultaneously without increase of toxicity. This indicated that delay of study treatment would be potentially more harmful to the patient, given the rapid growth of this tumor entity.

15 October 2021	Protocol Amendment 6 was performed for adjustment of statistical plan for cohort 2b. The original plan was a one-stage A'Hern design with response proportions $0 = 0.075$ and $1 = 0.2$, $\alpha = 0.1$ and $\beta = 0.10$. Here, 51 evaluable patients were required, the null hypothesis $0: \leq 0.075$ would have been rejected if at least 7 responses in 51 patients were observed. By the same assumptions and expectation as described above, 59 ($\approx 51/0.9$) patients would be needed to be enrolled, thus 563 patients were expected to be screened in total to include 59 TMB high patients. As recruitment into the trial was slower than anticipated, the patient number was reduced within a modified statistic which still provided sufficient power for primary endpoint analysis. Additionally, some clarifications concerning the screening biopsy in cohort 2b were provided.
19 December 2022	With Protocol Amendment 7, timelines for conduct of the trial were modified and enrolment for cohort 2b was closed, as the cohort was fully recruited.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 December 2017	The cohort 2a (SCLC all-comer) was stopped for recruitment after eighteen patients had been enrolled as two treatment-related deaths had occurred. Cohort 2b was opened for SCLC patients with high tumor mutation burden in October 2018.	30 October 2018
25 April 2019	The cohort 1 (NSCLC) had to be terminated early due to lack of feasibility as there was a high dropout rate (50%) from treatment part A to part B. This was partially due to either rapid disease progression which led to physicians' decision of performing treatment outside the trial and partially due to immune-related adverse events in treatment part A that would not allow therapy-escalation by adding ipilimumab. Furthermore, during the course of the trial the anti-PD-1 antibody pembrolizumab was approved in 1st line treatment of NSCLC, either alone or in combination with chemotherapy. This approval altered the basic conditions for the conduct of the trial as only immunotherapy-naïve were allowed to be enrolled into this cohort.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Cohort 1: terminated early
Cohort 2a: terminated early

Notes:

Online references

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