Clinical trial results:
A Phase 3, Randomized, Open-label Study to Compare Adjuvant Immunotherapy of Bempegaldesleukin Combined with Nivolumab Versus Nivolumab After Complete Resection of Melanoma in Patients at High Risk for Recurrence (PIVOT-12).

Summary

EudraCT number	2020-000917-34
Trial protocol	CZ FR GR PL AT PT DE NL GB IT RO
Global end of trial date	22 September 2022

Results information

Result version number	v1 (current)
This version publication date	16 March 2023
First version publication date	16 March 2023

Trial information

Trial identification

Sponsor protocol code	20-214-29/CA045-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04410445
WHO universal trial number (UTN)	-
Other trial identifiers	US IND No: 125471

Notes:

Sponsors

Sponsor organisation name	Nektar Therapeutics
Sponsor organisation address	455 Mission Bay Boulevard South, San Francisco, United States, CA 94158
Public contact	Clinical Trial Information Desk, Nektar Therapeutics, Nektar Therapeutics, +1 855 482 8676, studyinquiry@nektar.com
Scientific contact	Clinical Trial Information Desk, Nektar Therapeutics, Nektar Therapeutics, +1 855 482 8676, studyinquiry@nektar.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 September 2022
Global end of trial reached?	Yes
Global end of trial date	22 September 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the efficacy, as measured by recurrence-free survival (RFS) by blinded independent central review (BICR), of bempegaldesleukin plus nivolumab versus nivolumab in patients with completely resected Stage IIIA (lymph node [LN] metastasis > 1 mm), Stage IIIB/C/D, or Stage IV (American Joint Committee on Cancer [AJCC] 8th edition) cutaneous melanoma with no evidence of disease (NED) who are at high risk for recurrence.

Protection of trial subjects:

The conduct of the study was consistent with the principles that have their origin in the Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with ICH GCP, as well as with any applicable regulatory authority, federal, state, and/or local laws and regulations. Patients were to be informed of all aspects of the study relevant to the patient's decision to participate, and the ICF was to be presented to each patient in the language in which the patient was fluent. Informed consent was obtained and documented by each patient or patient's legal representative prior to any protocol-specific procedures. Signed ICFs were retained by the Investigator with the study records. Each patient/legal representative was given a copy of the signed and dated ICF.

Background therapy:

Not applicable

Evidence for comparator:

Bempegaldesleukin + nivolumab were compared with nivolumab after complete resection of melanoma in patients at high risk for recurrence. Nivolumab 480 mg IV infusion q4w (or 6.0 mg/kg IV infusion q4w for patients < 40 kg) were administrated as reference therapy.

Actual start date of recruitment	28 July 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Spain: 84
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Austria: 21
Country: Number of subjects enrolled	Czechia: 20
Country: Number of subjects enrolled	France: 49

Country: Number of subjects enrolled	Germany: 90
Country: Number of subjects enrolled	Greece: 43
Country: Number of subjects enrolled	Italy: 74
Country: Number of subjects enrolled	Australia: 77
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	New Zealand: 33
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	United States: 141
Worldwide total number of subjects	765
EEA total number of subjects	439

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)	546
From 65 to 84 years	217
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

774 subjects were enrolled in the study (386 in the bempegaldesleukin + nivolumab arm and 388 in the nivolumab arm). 9 of 774 subjects were not treated. 765 subjects were randomly assigned in a 1:1 ratio to 1 of 2 treatment arms:
- Arm A: bempegaldesleukin + nivolumab every 3 weeks (q3w)
- Arm B: nivolumab monotherapy every 4 weeks (q4w).

Pre-assignment

Screening details:

This study was divided into a Screening period, a Treatment period, and a Long-Term Follow-Up period. The subjects who met all the inclusion and none of the exclusion criteria were selected to participate in the study.

Period 1

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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: bempegaldesleukin + nivolumab

Arm description:

Bempegaldesleukin (NKTR-214) 0.006 mg/kg intravenous (IV) infusion + nivolumab 360 mg IV infusion (or 4.5 mg/kg IV infusion q3w for patients < 40 kg) were administrated every 3 weeks (q3w).

Arm type	Experimental
Investigational medicinal product name	Bempegaldesleukin
Investigational medicinal product code	
Other name	NKTR-214
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bempegaldesleukin 0.006 mg/kg intravenous (IV) infusion q3w. NKTR-214 was provided in 1.0 mg and 0.5 mg vials.

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

Dosage and administration details:

Nivolumab 360 mg IV infusion q3w (or 4.5 mg/kg IV infusion q3w for patients < 40 kg).

Arm title	Arm B: nivolumab monotherapy

Arm description:

Nivolumab 480 mg IV infusion (or 6.0 mg/kg IV infusion q4w for patients < 40 kg) was administrated every 4 weeks (q4w).

Arm type	Active comparator

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

Dosage and administration details:

Nivolumab 480 mg IV infusion q4w (or 6.0 mg/kg IV infusion q4w for patients < 40 kg).

Number of subjects in period 1	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy
Started	378	387
Completed	348	363
Not completed	30	24
Consent withdrawn by subject	27	15
Lost to follow-up	3	9

Baseline characteristics

Reporting groups

Reporting group title	Arm A: bempegaldesleukin + nivolumab

Reporting group description:

Bempegaldesleukin (NKTR-214) 0.006 mg/kg intravenous (IV) infusion + nivolumab 360 mg IV infusion (or 4.5 mg/kg IV infusion q3w for patients < 40 kg) were administrated every 3 weeks (q3w).

Reporting group title	Arm B: nivolumab monotherapy

Reporting group description:

Nivolumab 480 mg IV infusion (or 6.0 mg/kg IV infusion q4w for patients < 40 kg) was administrated every 4 weeks (q4w).

Reporting group values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy	Total
Number of subjects	378	387	765
Age categorical Units: Subjects			
Adults (18-64 years)	268	278	546
From 65-84 years	109	108	217
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	55	56	
standard deviation	± 14.21	± 13.45	-
Gender categorical Units: Subjects			
Female	162	148	310
Male	216	239	455

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 765 patients who received at least 1 dose of study drug (378 patients in the bempegaldesleukin + nivolumab arm; 387 patients in the nivolumab arm) were included in Safety population. Demographic and baseline characteristics are summarized for Safety population. All analyses were performed on the Safety Population.

Reporting group values	Safety Population		
Number of subjects	765		
Age categorical Units: Subjects			
Adults (18-64 years)	546		
From 65-84 years	217		
85 years and over	2		

Age continuous Units: years			
arithmetic mean	55.5		
standard deviation	± 13.83		
Gender categorical Units: Subjects			
Female	310		
Male	455		

End points

End points reporting groups

Reporting group title	Arm A: bempegaldesleukin + nivolumab

Reporting group description:

Bempegaldesleukin (NKTR-214) 0.006 mg/kg intravenous (IV) infusion + nivolumab 360 mg IV infusion (or 4.5 mg/kg IV infusion q3w for patients < 40 kg) were administrated every 3 weeks (q3w).

Reporting group title	Arm B: nivolumab monotherapy

Reporting group description:

Nivolumab 480 mg IV infusion (or 6.0 mg/kg IV infusion q4w for patients < 40 kg) was administrated every 4 weeks (q4w).

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 765 patients who received at least 1 dose of study drug (378 patients in the bempegaldesleukin + nivolumab arm; 387 patients in the nivolumab arm) were included in Safety population. Demographic and baseline characteristics are summarized for Safety population. All analyses were performed on the Safety Population.

Primary: Recurrence-free Survival (RFS) by BICR

End point title	Recurrence-free Survival (RFS) by BICR[1]

End point description:

RFS, defined as the time between the date of randomization and the date of first reccurence (local, regional, or distant metastasis by BICR), a new primary melanoma (by BICR), or all-cause death, whichever occurred first. For this outcome measure, zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early due to the closure of the bempegaldesleukin clinical development program due to lack of enhanced efficacy being observed in combination with nivolumab therapy over nivolumab monotherapy for metastatic melanoma. As consequence, no aggregate blinded independent central review data were available; no comparative analysis between bempegaldesleukin + nivolumab arm vs nivolumab arm were conducted for this efficacy endpoint.

End point type	Primary

End point timeframe:

Patients were treated up to approximately 1 year (maximum of 17 cycles for the bempegaldesleukin + nivolumab arm and 13 cycles for the nivolumab arm).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the early termination of the study, as a consequence of the closure of the bempegaldesleukin clinical program, no BICR data were transferred and analysed, and primary endpoint data was not evaluable.

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy	Safety Population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: Time				
median (full range (min-max))	(to)	(to)	(to)	

Notes:

[2] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

[3] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

[4] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) is defined as the time between the date of randomization and the date of death due to any cause. For this outcome measure, the results were not estimable due to insufficient number of events. The number 999 indicates the result was not estimable due to insufficient number of events. The study was terminated early due to the closure of the bempegaldesleukin clinical development program due to lack of enhanced efficacy being observed in combination with nivolumab therapy over nivolumab monotherapy for metastatic melanoma. No comparative analyses between bempegaldesleukin + nivolumab arm vs nivolumab arm were conducted for this efficacy endpoint.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378[5]	387[6]		
Units: Months				
number (confidence interval 95%)	999 (16.9 to 999)	999 (999 to 999)		

Notes:

[5] - Median and upper CI was not estimable due to insufficient number of events.

[6] - Median and 95% CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Metastasis-free Survival (DMFS) by Investigator

End point title	Distant Metastasis-free Survival (DMFS) by Investigator

End point description:

For this outcome measure, the results were not estimable due to insufficient number of events. Distant Metastasis-free Survival (DMFS) measured by Investigator in patients who have stage IIIA (LN Metastasis > 1 mm) or IIIB/C/D Melanoma at study entry. Metastasis Free Survival is defined as the time between the date of randomization and the date of first distant metastasis or date of death due to any cause. The number 999 indicate the result was not estimable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	355		
Units: Months				
number (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression After the Next Line of Treatment

End point title	Time to Disease Progression After the Next Line of Treatment

End point description:

Time to Disease Progression After the Next Line of Treatment measured for study patients following discontinuation of bempegaldesleukin plus nivolumab versus nivolumab. For this outcome measure, zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early due to the closure of the bempegaldesleukin clinical development program due to lack of enhanced efficacy being observed in combination with nivolumab therapy over nivolumab monotherapy for metastatic melanoma. No comparative analyses between bempegaldesleukin + nivolumab arm vs nivolumab arm were conducted for this efficacy endpoint.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: percent				
number (not applicable)				
Overall Number of Participants Analyzed				

Notes:

[7] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

[8] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence-free Survival (RFS) by Investigator

End point title	Recurrence-free Survival (RFS) by Investigator

End point description:

RFS by Investigator Will be Measured Similarly to the Primary Endpoint, But Recurrence and New Primary Melanoma Will be Decided by the Investigator. For this outcome measure, the results were not estimable due to insufficient number of events. The number 999 indicates the result was not estimable

due to insufficient number of events. The study was terminated early due to the closure of the bempegaldesleukin clinical development program due to lack of enhanced efficacy being observed in combination with nivolumab therapy over nivolumab monotherapy for metastatic melanoma. As a consequence no comparative analyses between bempegaldesleukin + nivolumab arm vs nivolumab arm were conducted for this efficacy endpoint.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378[9]	387[10]		
Units: Months				
number (confidence interval 95%)	999 (999 to 999)	999 (14.3 to 999)		

Notes:

[9] - Median and 95% CI was not estimable due to insufficient number of events.

[10] - Median and upper CI was not estimable due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Reported Outcomes

End point title	Patient Reported Outcomes

End point description:

Patient Reported Outcomes measured by changes from baseline in scores for the Global Health/Quality of Life and Physical Functioning Subscales of the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire.
The EORTC QLQ-C30 comprises 30 items (i.e. single questions), 24 of which are aggregated into nine multi-item scales, that is, five functioning scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting) and one global health status scale. Due to the study termination, results for the mean change from baseline for GH/QoL and the physical functioning subscale were analyzed at approximately 6 months of treatment.

End point type	Secondary

End point timeframe:

Approximately up to 6 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378	387		
Units: Score on a scale				
arithmetic mean (standard deviation)				
GH/QoL	-3.71 (± 16.933)	-0.66 (± 17.871)		

Physical Functioning Subscale	-2.41 (± 12.168)	-1.13 (± 12.606)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point description:

To evaluate safety and tolerability of (NKTR-214) 0.006 mg/kg in combination with nivolumab 360 mg IV infusion (or 4.5 mg/kg IV infusion q3w for patients <40 kg) and nivolumab 480 mg IV infusion (or 6.0 mg/kg IV infusion q4w for patients < 40 kg). Treatment-emergent adverse event (TEAE) is defined as an AE that was not present prior to treatment with study drug but appeared following treatment or was present at treatment start date but worsened during treatment-emergent period. The treatment-emergent period is defined as the period from the date of the first dose of study drug up to 30 days after the date of the last dose of study drug or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

End point type	Secondary

End point timeframe:

Approximately up to 21 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	378	387		
Units: Participants				
Subjects who had a TEAE	370	330		
Subjects who had a Serious TEAE	74	33		
Subjects who had a TEAE of Grade 3 or Higher	120	50		
Subjects who had a TEAE Leading to Death	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Metastasis-free Survival (DMFS) by Blinded Independent Central Review (BICR)

End point title	Distant Metastasis-free Survival (DMFS) by Blinded Independent Central Review (BICR)

End point description:

Distant Metastasis-free Survival (DMFS) measured by Blinded Independent Central Review (BICR) in Patients Who Have Stage IIIA (LN Metastasis > 1 mm) or IIIB/C/D Melanoma at Study Entry. Distant Metastasis Free Survival is defined as the time between the date of randomization and the date of first distant metastasis or date of death due to any cause. For this outcome measure, zero (”0”) participants were analysed in each Arm/Group.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Months				
number (not applicable)				
Overall Number of Participants Analyzed				

Notes:

[11] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

[12] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

Statistical analyses

No statistical analyses for this end point

Secondary: The Predictive Strength of PD-L1 Expression as a Biomarker

End point title	The Predictive Strength of PD-L1 Expression as a Biomarker

End point description:

The Predictive Strength of PD-L1 Expression as a Biomarker was measured by the endpoint RFS by BICR based on PD-L1 expression level. For this outcome measure, zero (”0”) participants were analysed in each Arm/Group. The study was terminated early due to the closure of the bempegaldesleukin clinical development program due to lack of enhanced efficacy being observed in combination with nivolumab therapy over nivolumab monotherapy for metastatic melanoma. As a consequence, no aggregate blinded independent central review data were available; no comparative analyses between bempegaldesleukin + nivolumab arm vs nivolumab arm were conducted for this efficacy endpoint.

End point type	Secondary

End point timeframe:

Up to 60 months

End point values	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Participants				
Overall Number of Participants Analyzed				

Notes:
[13] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.
[14] - Zero (”0”) participants were analyzed in each Arm/Group. The study was terminated early.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be reported starting immediately after the patient has been administered the first dose of study drug(s) until 100 days (+/- 7 days) after the last dose of all study drug(s).

Adverse event reporting additional description:

All ongoing non-serious AEs will be followed until resolution, the patient is lost to follow-up, patient death, or until the last Safety Follow-Up Visit. If the AE has not completely resolved by the last Safety Follow-Up Visit, the final outcome of these ongoing AEs will be captured.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Arm A: bempegaldesleukin + nivolumab

Reporting group description:

Bempegaldesleukin (NKTR-214) 0.006 mg/kg intravenous (IV) infusion + nivolumab 360 mg IV infusion (or 4.5 mg/kg IV infusion q3w for patients < 40 kg) were administrated every 3 weeks (q3w).

Reporting group title	Arm B: nivolumab monotherapy

Reporting group description:

Nivolumab 480 mg IV infusion (or 6.0 mg/kg IV infusion q4w for patients < 40 kg) was administrated every 4 weeks (q4w).

Serious adverse events	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 378 (19.58%)	33 / 387 (8.53%)	
number of deaths (all causes)	9	4	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 378 (0.26%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flushing			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor venous access			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
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			
Pyrexia			
subjects affected / exposed	6 / 378 (1.59%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	6 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chills			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	3 / 378 (0.79%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary permeability increased			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 378 (0.26%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			

subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 378 (0.26%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haemorrhage			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			

subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 378 (1.06%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	3 / 378 (0.79%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuropericarditis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune myocarditis			

subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 378 (0.79%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune neuropathy			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilia			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness transient			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 378 (0.79%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Autoimmune pancreatitis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	3 / 378 (0.79%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 378 (0.26%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic mass			

subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (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			
Acute kidney injury			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune nephritis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 378 (0.53%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 378 (0.26%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Primary adrenal insufficiency			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune myositis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	3 / 378 (0.79%)	2 / 387 (0.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	1 / 378 (0.26%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 378 (0.26%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 378 (0.26%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 378 (0.00%)	2 / 387 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 378 (0.53%)	0 / 387 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 378 (0.00%)	1 / 387 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: bempegaldesleukin + nivolumab	Arm B: nivolumab monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	369 / 378 (97.62%)	329 / 387 (85.01%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	40 / 378 (10.58%)	3 / 387 (0.78%)	
occurrences (all)	65	5	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	160 / 378 (42.33%)	22 / 387 (5.68%)	
occurrences (all)	417	27	
Fatigue			
subjects affected / exposed	154 / 378 (40.74%)	112 / 387 (28.94%)	
occurrences (all)	262	128	
Influenza like illness			

subjects affected / exposed	114 / 378 (30.16%)	11 / 387 (2.84%)	
occurrences (all)	327	13	
Asthenia			
subjects affected / exposed	70 / 378 (18.52%)	38 / 387 (9.82%)	
occurrences (all)	136	50	
Chills			
subjects affected / exposed	55 / 378 (14.55%)	7 / 387 (1.81%)	
occurrences (all)	80	9	
Face oedema			
subjects affected / exposed	21 / 378 (5.56%)	1 / 387 (0.26%)	
occurrences (all)	35	1	
Oedema peripheral			
subjects affected / exposed	21 / 378 (5.56%)	7 / 387 (1.81%)	
occurrences (all)	42	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	52 / 378 (13.76%)	16 / 387 (4.13%)	
occurrences (all)	58	18	
Dyspnoea			
subjects affected / exposed	40 / 378 (10.58%)	14 / 387 (3.62%)	
occurrences (all)	56	14	
Nasal congestion			
subjects affected / exposed	22 / 378 (5.82%)	4 / 387 (1.03%)	
occurrences (all)	31	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	26 / 378 (6.88%)	22 / 387 (5.68%)	
occurrences (all)	30	23	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	37 / 378 (9.79%)	24 / 387 (6.20%)	
occurrences (all)	47	25	
Aspartate aminotransferase increased			
subjects affected / exposed	27 / 378 (7.14%)	22 / 387 (5.68%)	
occurrences (all)	36	22	
Nervous system disorders			

Headache			
subjects affected / exposed	85 / 378 (22.49%)	46 / 387 (11.89%)	
occurrences (all)	139	50	
Dizziness			
subjects affected / exposed	37 / 378 (9.79%)	18 / 387 (4.65%)	
occurrences (all)	47	21	
Paraesthesia			
subjects affected / exposed	20 / 378 (5.29%)	4 / 387 (1.03%)	
occurrences (all)	24	4	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	45 / 378 (11.90%)	7 / 387 (1.81%)	
occurrences (all)	53	7	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	106 / 378 (28.04%)	50 / 387 (12.92%)	
occurrences (all)	182	57	
Diarrhoea			
subjects affected / exposed	101 / 378 (26.72%)	68 / 387 (17.57%)	
occurrences (all)	138	94	
Vomiting			
subjects affected / exposed	52 / 378 (13.76%)	17 / 387 (4.39%)	
occurrences (all)	85	22	
Abdominal pain upper			
subjects affected / exposed	34 / 378 (8.99%)	12 / 387 (3.10%)	
occurrences (all)	39	12	
Dry mouth			
subjects affected / exposed	33 / 378 (8.73%)	15 / 387 (3.88%)	
occurrences (all)	34	15	
Abdominal pain			
subjects affected / exposed	24 / 378 (6.35%)	18 / 387 (4.65%)	
occurrences (all)	33	20	
Constipation			
subjects affected / exposed	23 / 378 (6.08%)	27 / 387 (6.98%)	
occurrences (all)	24	28	
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	95 / 378 (25.13%)	54 / 387 (13.95%)	
occurrences (all)	119	57	
Rash			
subjects affected / exposed	75 / 378 (19.84%)	34 / 387 (8.79%)	
occurrences (all)	103	35	
Rash maculo-papular			
subjects affected / exposed	55 / 378 (14.55%)	21 / 387 (5.43%)	
occurrences (all)	103	35	
Erythema			
subjects affected / exposed	46 / 378 (12.17%)	4 / 387 (1.03%)	
occurrences (all)	60	4	
Dry skin			
subjects affected / exposed	31 / 378 (8.20%)	9 / 387 (2.33%)	
occurrences (all)	34	9	
Pruritus generalised			
subjects affected / exposed	37 / 378 (9.79%)	9 / 387 (2.33%)	
occurrences (all)	46	9	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	80 / 378 (21.16%)	35 / 387 (9.04%)	
occurrences (all)	80	35	
Hypothyroidism			
subjects affected / exposed	65 / 378 (17.20%)	39 / 387 (10.08%)	
occurrences (all)	66	40	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	83 / 378 (21.96%)	49 / 387 (12.66%)	
occurrences (all)	140	54	
Myalgia			
subjects affected / exposed	67 / 378 (17.72%)	23 / 387 (5.94%)	
occurrences (all)	110	25	
Back pain			
subjects affected / exposed	33 / 378 (8.73%)	15 / 387 (3.88%)	
occurrences (all)	50	17	
Pain in extremity			

subjects affected / exposed	23 / 378 (6.08%)	15 / 387 (3.88%)	
occurrences (all)	31	15	
Musculoskeletal pain			
subjects affected / exposed	19 / 378 (5.03%)	7 / 387 (1.81%)	
occurrences (all)	28	10	
Infections and infestations			
Coronavirus infection			
subjects affected / exposed	49 / 378 (12.96%)	47 / 387 (12.14%)	
occurrences (all)	49	50	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	53 / 378 (14.02%)	13 / 387 (3.36%)	
occurrences (all)	75	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2021	• Added DMFS by BICR as a secondary objective of the study and associated data analysis. • Elevated time to disease progression after the next line of treatment from an exploratory objective to a secondary objective of the study. • Clarified the definition for end of study. • Clarified that patients ≥ 12 years of age at the time of signing the informed consent are eligible to participate in the study, except where local regulations, countries and/or institutional policies do not allow for patients < 18 years of age (adolescents) to participate. • Modified inclusion criterion 11.c to indicate women should use "effective methods" of contraception. • Modified exclusion criterion 19 to extract Criterion 19b for TIA/CVA to its own exclusion criterion 20. • Added a new section for measures of treatment compliance. • Specified the EORTC QLQ-C30 and EQ-5D-5L to be administered before any other study-related procedures, with the EORTC QLQ-C30 assessed before the EQ-5D-5L. • Removed medical resource utilization and healthcare economics from study assessments. • Clarified PK and immunogenicity blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion and clarified the sample analysis methodologies. • Added blood samples to be collected for exploratory biomarker analysis to characterize TIA events and clarified blood samples should be collected as close as possible to the new CVA or TIA event. • Reorganized monitoring and management of bempegaldesleukin-induced eosinophilia; updated language characterizing eosinophilia in patients receiving bempegaldesleukin; added language to describe isolated cases of hypereosinophilic syndrome and drug reaction with eosinophilia. • Other changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Not applicable

Notes: