Clinical trial results:
A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN 144) for Treatment of Patients with Metastatic Melanoma

Summary

EudraCT number	2017-000760-15
Trial protocol	GB HU DE ES FR IT
Global end of trial date	24 October 2024

Results information

Result version number	v1 (current)
This version publication date	12 November 2025
First version publication date	12 November 2025

Trial information

Trial identification

Sponsor protocol code	C-144-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02360579
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Iovance Biotherapeutics, Inc.
Sponsor organisation address	825 Industrial Rd Suite 100, San Carlos, United States, 94070
Public contact	Rana Fiaz, Executive Medical Director, Iovance Biotherapeutics, Inc., +1 844-845-4682, Clinical.Inquiries@iovance.com
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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	05 March 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 October 2024
Global end of trial reached?	Yes
Global end of trial date	24 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy of LN-144 in patients with unresectable or metastatic melanoma using the ORR, as assessed by the IRC per RECIST v1.1

Protection of trial subjects:

This study was conducted in compliance with the Good Clinical Practice (GCP) guidelines and adhered to applicable national and/or local statutes and regulations concerning ethical committee review, informed consent, and the protection of human subjects involved in clinical trials.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	United States: 163
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	220
EEA total number of subjects	46

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)	175
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Cohort 3 patients had progressed following initial treatment in Cohorts 1, 2, 4 and then were retreated with a second TIL regimen. For sections below where no results are presented for this cohort, these patients are accounted for in their original cohort.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Cohort 1

Arm description:

Non-cryopreserved TIL (LN-144, Gen 1)

A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with TIL followed by IL-2.

Arm type	Experimental
Investigational medicinal product name	Non-cryopreserved TIL (Gen 1)
Investigational medicinal product code	LN-144
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Infusion

Dosage and administration details:

Non-cryopreserved TIL (Gen 1) is a preparation of TIL derived from an individual patient's tumor for patient-directed immunotherapy. Non-cryopreserved TIL is provided as a single dose for infusion containing 1 × 10^9 to 150 × 10^9 viable cells. Patients were to receive the full dose of product that was manufactured. Lot numbers are patient-specific.

Arm title	Cohort 2

Arm description:

Cryopreserved lifileucel (LN-144) (Gen 2 infusion product).

Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.

Arm type	Experimental
Investigational medicinal product name	Lifileucel (Gen 2)
Investigational medicinal product code	LN-144
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Infusion

Dosage and administration details:

Lifileucel is a preparation of TIL derived from an individual patient's tumor for patient-directed immunotherapy. Lifileucel is provided as a single dose for infusion containing 1 × 10^9 to 150 × 10^9 viable cells suspended in a cryopreservation medium. Patients were to receive the full dose of product that was manufactured. Lot numbers are patient-specific.

Arm title	Cohort 3 (Retreatment Cohort)

Arm description:

Retreatment cohort: patients from Cohort 1, Cohort 2 or Cohort 4 may rescreen for a second TIL regimen therapy if they meet all Inclusion and Exclusion Criteria (except exclusion criterion b).

Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.

Arm type	Experimental
Investigational medicinal product name	Lifileucel (Gen 2)
Investigational medicinal product code	LN-144
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Infusion

Dosage and administration details:

Lifileucel is a preparation of TIL derived from an individual patient's tumor for patient-directed immunotherapy. Lifileucel is provided as a single dose for infusion containing 1 × 10^9 to 150 × 10^9 viable cells suspended in a cryopreservation medium. Patients were to receive the full dose of product that was manufactured. Lot numbers are patient-specific.

Arm title	Cohort 4

Arm description:

Cryopreserved lifileucel (LN-144) (Gen 2 infusion product)

Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.

Arm type	Experimental
Investigational medicinal product name	Lifileucel (Gen 2)
Investigational medicinal product code	LN-144
Other name	
Pharmaceutical forms	Suspension for suspension for injection
Routes of administration	Infusion

Dosage and administration details:

Lifileucel is a preparation of TIL derived from an individual patient's tumor for patient-directed immunotherapy. Lifileucel is provided as a single dose for infusion containing 1 × 10^9 to 150 × 10^9 viable cells suspended in a cryopreservation medium. Patients were to receive the full dose of product that was manufactured. Lot numbers are patient-specific.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3 (Retreatment Cohort)
Started	31	78	12
Completed	0	14	1
Not completed	31	64	11
Consent withdrawn by subject	-	-	-
Death	16	49	11
Unknown	7	-	-
Did not receive TIL	8	11	-
Lost to follow-up	-	4	-

Number of subjects in period 1	Cohort 4
Started	111

Completed	14
Not completed	97
Consent withdrawn by subject	3
Death	71
Unknown	-
Did not receive TIL	22
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Non-cryopreserved TIL (LN-144, Gen 1) A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with TIL followed by IL-2.	
Reporting group title	Cohort 2
Reporting group description:	
Cryopreserved lifileucel (LN-144) (Gen 2 infusion product). Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.	
Reporting group title	Cohort 3 (Retreatment Cohort)
Reporting group description:	
Retreatment cohort: patients from Cohort 1, Cohort 2 or Cohort 4 may rescreen for a second TIL regimen therapy if they meet all Inclusion and Exclusion Criteria (except exclusion criterion b). Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.	
Reporting group title	Cohort 4
Reporting group description:	
Cryopreserved lifileucel (LN-144) (Gen 2 infusion product) Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.	

Reporting group values	Cohort 1	Cohort 2	Cohort 3 (Retreatment Cohort)
Number of subjects	31	78	12
Age categorical			
Total Number of 220 includes Cohort 1, 2, and 4. Cohort 3 is a retreatment cohort.			
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)	29	62	11
From 65-84 years	2	16	1
85 years and over	0	0	0
Age continuous			
Units: years			
median	52	55	52
full range (min-max)	28 to 72	20 to 79	29 to 66

Gender categorical			
Total Number of 220 includes Cohort 1, 2, and 4. Cohort 3 is a retreatment cohort.			
Units: Subjects			
Female	14	37	3
Male	17	41	9

Reporting group values	Cohort 4	Total	
Number of subjects	111	220	
Age categorical			
Total Number of 220 includes Cohort 1, 2, and 4. Cohort 3 is a retreatment cohort.			
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)	84	175	
From 65-84 years	27	45	
85 years and over	0	0	
Age continuous			
Units: years			
median	55		
full range (min-max)	25 to 74	-	
Gender categorical			
Total Number of 220 includes Cohort 1, 2, and 4. Cohort 3 is a retreatment cohort.			
Units: Subjects			
Female	51	102	
Male	60	118	

End points

End points reporting groups

Reporting group title	Cohort 1

Reporting group description:

Non-cryopreserved TIL (LN-144, Gen 1)

A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with TIL followed by IL-2.

Reporting group title	Cohort 2

Reporting group description:

Cryopreserved lifileucel (LN-144) (Gen 2 infusion product).

Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.

Reporting group title	Cohort 3 (Retreatment Cohort)

Reporting group description:

Retreatment cohort: patients from Cohort 1, Cohort 2 or Cohort 4 may rescreen for a second TIL regimen therapy if they meet all Inclusion and Exclusion Criteria (except exclusion criterion b).

Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.

Reporting group title	Cohort 4

Reporting group description:

Cryopreserved lifileucel (LN-144) (Gen 2 infusion product)

Lifileucel: A tumor sample is resected from each patient and cultured ex vivo to expand the population of tumor infiltrating lymphocytes. After lymphodepletion, patients are infused with lifileucel followed by IL-2.

Subject analysis set title	Pooled Cohorts 2 & 4
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set is defined as participants who received the lifileucel infusion that met product manufacturing specifications.

Data from Cohorts 2 and 4 participants in full analysis set are pooled to evaluate efficacy of cryopreserved TIL product.

Primary: Disease Assessment for Objective Response Rate

End point title	Disease Assessment for Objective Response Rate[1][2]

End point description:

The Full Analysis Set is defined as patients who received the lifileucel infusion that met product manufacturing specifications.

Evaluate the efficacy of LN-144 in patients with unresectable or metastatic melanoma using the objective response rate (ORR), as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

End point type	Primary

End point timeframe:

Every 6 weeks for 6 months, then every 3 months for a maximum of 60 months

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: No comparative statistical analysis has been performed for this primary endpoint due to single arm study design.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analyses of efficacy and safety data were performed for Cohort 2, Cohort 4, and pooled Cohorts 2 and 4 in order to evaluate cryopreserved TIL product. Cohort 3 patients had progressed following initial treatment in Cohorts 1, 2, 4 and then were retreated with a second TIL regimen. These patients are accounted for below in their original cohorts. Tumor assessments for Cohort 1 patients were not assessed by the IRC.

End point values	Cohort 2	Cohort 4	Pooled Cohorts 2 & 4	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	66	87	153	
Units: %				
number (confidence interval 95%)	34.8 (23.5 to 47.6)	28.7 (19.5 to 39.4)	31.4 (24.1 to 39.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Assessment for Duration of Response

End point title	Disease Assessment for Duration of Response[3]

End point description:

Evaluate the efficacy endpoints of duration of response (DOR) by the IRC and by the investigator per RECIST v1.1.

Due to the high concordance between the objective response as assessed by the Investigator and the IRC (89.4% in Cohort 2 and 92.0% in Cohort 4), the efficacy results as assessed by the IRC are presented.

End point type	Secondary

End point timeframe:

Every 6 weeks for 6 months, then every 3 months for a maximum of 60 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analyses of efficacy and safety data were performed for Cohort 2, Cohort 4, and pooled Cohorts 2 and 4 in order to evaluate cryopreserved TIL product. Cohort 3 patients had progressed following initial treatment in Cohorts 1, 2, 4 and then were retreated with a second TIL regimen. These patients are accounted for in their original cohorts. Tumor assessments for Cohort 1 patients were not assessed by the IRC.

End point values	Cohort 2	Cohort 4	Pooled Cohorts 2 & 4	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	23[4]	25	48	
Units: Months				
median (full range (min-max))	0 (0 to 0)	10.4 (1.4 to 56.4)	36.5 (1.4 to 58.7)	

Notes:

[4] - Median DOR was not reached in Cohort 2. Full range (Min - Max): 1.4 to 58.7 months.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Assessment for Disease Control Rate

End point title	Disease Assessment for Disease Control Rate[5]

End point description:

Evaluate the efficacy endpoints of disease control rate (DCR) as assessed by the IRC and by the investigator per RECIST v1.1.

Due to the high concordance between the objective response as assessed by the Investigator and the IRC (89.4% in Cohort 2 and 92.0% in Cohort 4), the efficacy results as assessed by the IRC are presented.

End point type	Secondary

End point timeframe:

Every 6 weeks for 6 months, then every 3 months for a maximum of 60 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analyses of efficacy and safety data were performed for Cohort 2, Cohort 4, and pooled Cohorts 2 and 4 in order to evaluate cryopreserved TIL product. Cohort 3 patients had progressed following initial treatment in Cohorts 1, 2, 4 and then were retreated with a second TIL regimen. These patients are accounted for in their original cohorts. Tumor assessments for Cohort 1 patients were not assessed by the IRC.

End point values	Cohort 2	Cohort 4	Pooled Cohorts 2 & 4	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	66	87	153	
Units: %				
number (confidence interval 95%)	72.7 (60.0 to 83.0)	82.8 (73.2 to 90.0)	78.4 (71.1 to 84.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Assessment for Progression-Free Survival

End point title	Disease Assessment for Progression-Free Survival[6]

End point description:

Evaluate the efficacy endpoints of progression-free survival (PFS) as assessed by the IRC and by the investigator per RECIST v1.1.

The Full Analysis Set is defined as patients who received the lifileucel infusion that met product manufacturing specifications. Due to the high concordance between the objective response as assessed by the Investigator and the IRC (89.4% in Cohort 2 and 92.0% in Cohort 4), the efficacy results as assessed by the IRC are presented.

End point type	Secondary

End point timeframe:

Every 6 weeks for 6 months, then every 3 months for a maximum of 60 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analyses of efficacy and safety data were performed for Cohort 2, Cohort 4, and pooled Cohorts 2 and 4 in order to evaluate cryopreserved TIL product. Cohort 3 patients had progressed following initial treatment in Cohorts 1, 2, 4 and then were retreated with a second TIL regimen. These patients are accounted for in their original cohorts. Tumor assessments for Cohort 1 patients were not assessed by the IRC.

End point values	Cohort 2	Cohort 4	Pooled Cohorts 2 & 4	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	66	87	153	
Units: months				
median (confidence interval 95%)	4.1 (2.8 to 8.4)	3.9 (2.8 to 4.9)	4.1 (2.8 to 4.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival[7]

End point description:

Measure Description Evaluate overall survival (OS).

The Full Analysis Set is defined as patients who received the lifileucel infusion that met product manufacturing specifications.

End point type	Secondary

End point timeframe:

Until death or up to 60 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analyses of efficacy and safety data were performed for Cohort 2, Cohort 4, and pooled Cohorts 2 and 4 in order to evaluate cryopreserved TIL product. Cohort 3 patients had progressed following initial treatment in Cohorts 1, 2, 4 and then were retreated with a second TIL regimen. These patients are accounted for in their original cohorts.

End point values	Cohort 2	Cohort 4	Pooled Cohorts 2 & 4	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	66	87	153	
Units: months				
median (confidence interval 95%)	15.6 (11.0 to 23.3)	12.7 (8.3 to 17.8)	13.9 (10.6 to 17.8)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment to end of follow-up (up to 5 years)

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs), clinical laboratory data assessments, serious adverse events (SAEs), and adverse events (AEs) were collected and evaluated for the duration of the study until resolution or permanent sequelae. The Safety Analysis Set is defined as patients who have received TIL infusion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Non-cryopreserved TIL (LN-144, Gen 1)

Reporting group title	Cohort 2

Reporting group description:

Cryopreserved lifileucel (LN-144) (Gen 2 infusion product)

Reporting group title	Cohort 3

Reporting group description:

Retreatment cohort: patients from Cohort 1, Cohort 2 or Cohort 4 may rescreen for a second TIL regimen therapy if they meet all Inclusion and Exclusion Criteria (except exclusion criterion b).

Reporting group title	Cohort 4

Reporting group description:

Cryopreserved lifileucel (LN-144) (Gen 2 infusion product)

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 23 (39.13%)	23 / 67 (34.33%)	2 / 12 (16.67%)
number of deaths (all causes)	18	49	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Tumour pain			

subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	0 / 12 (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
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Embolism			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Hypotension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Shock			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Venous thrombosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Fatigue			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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

Pyrexia			
subjects affected / exposed	1 / 23 (4.35%)	2 / 67 (2.99%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	0 / 12 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytokine release syndrome			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Hypoxia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	0 / 12 (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	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Pulmonary embolism			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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 oedema			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Respiratory failure			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Delirium			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Depression			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Arrhythmia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Atrial fibrillation			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Cerebrovascular accident			

subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Encephalopathy			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	0 / 12 (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
Neuropathy peripheral			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Spinal cord compression			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	3 / 23 (13.04%)	6 / 67 (8.96%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	1 / 23 (4.35%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Thrombocytopenia			
subjects affected / exposed	3 / 23 (13.04%)	4 / 67 (5.97%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 6	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Colitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Haematochezia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Melaena			

subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Nausea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	0 / 12 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	0 / 12 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	0 / 12 (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
Oliguria			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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

Encephalitis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Pneumonia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	0 / 12 (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
Sepsis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Viral infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	0 / 12 (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
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	0 / 12 (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
Decreased appetite			

subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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
Hypophosphataemia			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	0 / 12 (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

Serious adverse events	Cohort 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 89 (34.83%)		
number of deaths (all causes)	71		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Shock				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chills				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cytokine release syndrome				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	3 / 89 (3.37%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	3 / 89 (3.37%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Atrial fibrillation				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain oedema				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vasogenic cerebral oedema			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Ascites				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal haemorrhage				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 89 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				

Rash			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oliguria			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Sepsis			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	67 / 67 (100.00%)	12 / 12 (100.00%)
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 23 (0.00%)	8 / 67 (11.94%)	2 / 12 (16.67%)
occurrences (all)	0	9	2

Flushing			
subjects affected / exposed	2 / 23 (8.70%)	4 / 67 (5.97%)	1 / 12 (8.33%)
occurrences (all)	3	4	1
Hypertension			
subjects affected / exposed	4 / 23 (17.39%)	9 / 67 (13.43%)	2 / 12 (16.67%)
occurrences (all)	4	12	2
Hypotension			
subjects affected / exposed	7 / 23 (30.43%)	24 / 67 (35.82%)	5 / 12 (41.67%)
occurrences (all)	8	26	5
Thrombophlebitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 23 (8.70%)	8 / 67 (11.94%)	0 / 12 (0.00%)
occurrences (all)	2	8	0
Chills			
subjects affected / exposed	15 / 23 (65.22%)	52 / 67 (77.61%)	9 / 12 (75.00%)
occurrences (all)	21	77	11
Fatigue			
subjects affected / exposed	8 / 23 (34.78%)	26 / 67 (38.81%)	1 / 12 (8.33%)
occurrences (all)	9	36	1
Malaise			
subjects affected / exposed	2 / 23 (8.70%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	2	4	0
Mucosal inflammation			
subjects affected / exposed	0 / 23 (0.00%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 23 (8.70%)	2 / 67 (2.99%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Oedema			
subjects affected / exposed	1 / 23 (4.35%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Oedema peripheral			

subjects affected / exposed	8 / 23 (34.78%)	17 / 67 (25.37%)	3 / 12 (25.00%)
occurrences (all)	8	20	3
Pain			
subjects affected / exposed	1 / 23 (4.35%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Pyrexia			
subjects affected / exposed	9 / 23 (39.13%)	39 / 67 (58.21%)	6 / 12 (50.00%)
occurrences (all)	10	110	11
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Hypersensitivity			
subjects affected / exposed	2 / 23 (8.70%)	0 / 67 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 23 (26.09%)	13 / 67 (19.40%)	0 / 12 (0.00%)
occurrences (all)	7	15	0
Dyspnoea			
subjects affected / exposed	4 / 23 (17.39%)	14 / 67 (20.90%)	0 / 12 (0.00%)
occurrences (all)	4	16	0
Epistaxis			
subjects affected / exposed	2 / 23 (8.70%)	1 / 67 (1.49%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Hypoxia			
subjects affected / exposed	1 / 23 (4.35%)	16 / 67 (23.88%)	2 / 12 (16.67%)
occurrences (all)	1	19	2
Lung disorder			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	2 / 23 (8.70%)	1 / 67 (1.49%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Oropharyngeal pain			

subjects affected / exposed	1 / 23 (4.35%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	1	4	0
Pleural effusion			
subjects affected / exposed	0 / 23 (0.00%)	6 / 67 (8.96%)	0 / 12 (0.00%)
occurrences (all)	0	10	0
Pleuritic pain			
subjects affected / exposed	0 / 23 (0.00%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Pulmonary oedema			
subjects affected / exposed	1 / 23 (4.35%)	2 / 67 (2.99%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Respiratory distress			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Tachypnoea			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Wheezing			
subjects affected / exposed	0 / 23 (0.00%)	6 / 67 (8.96%)	0 / 12 (0.00%)
occurrences (all)	0	7	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 23 (0.00%)	5 / 67 (7.46%)	0 / 12 (0.00%)
occurrences (all)	0	6	0
Confusional state			
subjects affected / exposed	1 / 23 (4.35%)	9 / 67 (13.43%)	1 / 12 (8.33%)
occurrences (all)	1	9	1
Delirium			
subjects affected / exposed	0 / 23 (0.00%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	0	5	0
Insomnia			
subjects affected / exposed	2 / 23 (8.70%)	6 / 67 (8.96%)	1 / 12 (8.33%)
occurrences (all)	2	6	1

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 23 (30.43%)	15 / 67 (22.39%)	4 / 12 (33.33%)
occurrences (all)	11	26	6
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 23 (21.74%)	19 / 67 (28.36%)	4 / 12 (33.33%)
occurrences (all)	7	31	9
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 23 (26.09%)	14 / 67 (20.90%)	2 / 12 (16.67%)
occurrences (all)	8	20	3
Blood bilirubin increased			
subjects affected / exposed	3 / 23 (13.04%)	5 / 67 (7.46%)	1 / 12 (8.33%)
occurrences (all)	5	10	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 23 (0.00%)	5 / 67 (7.46%)	1 / 12 (8.33%)
occurrences (all)	0	7	1
Blood creatinine increased			
subjects affected / exposed	1 / 23 (4.35%)	5 / 67 (7.46%)	2 / 12 (16.67%)
occurrences (all)	1	5	3
Breath sounds abnormal			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	1 / 12 (8.33%)
occurrences (all)	0	3	6
International normalised ratio increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Urine output decreased			
subjects affected / exposed	0 / 23 (0.00%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Weight decreased			
subjects affected / exposed	3 / 23 (13.04%)	9 / 67 (13.43%)	3 / 12 (25.00%)
occurrences (all)	5	17	4

Weight increased			
subjects affected / exposed	1 / 23 (4.35%)	16 / 67 (23.88%)	1 / 12 (8.33%)
occurrences (all)	1	27	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	1 / 23 (4.35%)	3 / 67 (4.48%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Skin laceration			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Atrial fibrillation			
subjects affected / exposed	1 / 23 (4.35%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Sinus tachycardia			
subjects affected / exposed	6 / 23 (26.09%)	10 / 67 (14.93%)	1 / 12 (8.33%)
occurrences (all)	8	16	1
Stress cardiomyopathy			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Supraventricular tachycardia			
subjects affected / exposed	0 / 23 (0.00%)	3 / 67 (4.48%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Tachycardia			
subjects affected / exposed	3 / 23 (13.04%)	23 / 67 (34.33%)	6 / 12 (50.00%)
occurrences (all)	5	25	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 23 (8.70%)	6 / 67 (8.96%)	1 / 12 (8.33%)
occurrences (all)	2	6	1

Headache			
subjects affected / exposed	3 / 23 (13.04%)	8 / 67 (11.94%)	0 / 12 (0.00%)
occurrences (all)	6	9	0
Lethargy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Presyncope			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 23 (78.26%)	46 / 67 (68.66%)	11 / 12 (91.67%)
occurrences (all)	53	146	35
Febrile neutropenia			
subjects affected / exposed	11 / 23 (47.83%)	30 / 67 (44.78%)	5 / 12 (41.67%)
occurrences (all)	11	33	5
Leukopenia			
subjects affected / exposed	12 / 23 (52.17%)	28 / 67 (41.79%)	2 / 12 (16.67%)
occurrences (all)	17	53	8
Lymphopenia			
subjects affected / exposed	6 / 23 (26.09%)	23 / 67 (34.33%)	3 / 12 (25.00%)
occurrences (all)	19	71	7
Neutropenia			
subjects affected / exposed	11 / 23 (47.83%)	37 / 67 (55.22%)	5 / 12 (41.67%)
occurrences (all)	20	55	5
Normocytic anaemia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Pancytopenia			
subjects affected / exposed	1 / 23 (4.35%)	5 / 67 (7.46%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Thrombocytopenia			

subjects affected / exposed	17 / 23 (73.91%)	60 / 67 (89.55%)	10 / 12 (83.33%)
occurrences (all)	54	220	31
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 23 (0.00%)	3 / 67 (4.48%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Vision blurred			
subjects affected / exposed	0 / 23 (0.00%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	0	4	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 23 (8.70%)	1 / 67 (1.49%)	1 / 12 (8.33%)
occurrences (all)	2	1	1
Abdominal pain			
subjects affected / exposed	2 / 23 (8.70%)	4 / 67 (5.97%)	1 / 12 (8.33%)
occurrences (all)	2	4	1
Abdominal pain upper			
subjects affected / exposed	0 / 23 (0.00%)	6 / 67 (8.96%)	0 / 12 (0.00%)
occurrences (all)	0	6	0
Constipation			
subjects affected / exposed	4 / 23 (17.39%)	13 / 67 (19.40%)	1 / 12 (8.33%)
occurrences (all)	4	15	1
Diarrhoea			
subjects affected / exposed	9 / 23 (39.13%)	19 / 67 (28.36%)	5 / 12 (41.67%)
occurrences (all)	14	27	5
Dry mouth			
subjects affected / exposed	1 / 23 (4.35%)	5 / 67 (7.46%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Dyspepsia			
subjects affected / exposed	2 / 23 (8.70%)	2 / 67 (2.99%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Nausea			

subjects affected / exposed	13 / 23 (56.52%)	16 / 67 (23.88%)	2 / 12 (16.67%)
occurrences (all)	18	17	2
Stomatitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	9 / 23 (39.13%)	14 / 67 (20.90%)	2 / 12 (16.67%)
occurrences (all)	14	18	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 23 (26.09%)	19 / 67 (28.36%)	0 / 12 (0.00%)
occurrences (all)	6	21	0
Dry skin			
subjects affected / exposed	3 / 23 (13.04%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	3	4	0
Erythema			
subjects affected / exposed	4 / 23 (17.39%)	4 / 67 (5.97%)	0 / 12 (0.00%)
occurrences (all)	4	4	0
Petechiae			
subjects affected / exposed	3 / 23 (13.04%)	2 / 67 (2.99%)	0 / 12 (0.00%)
occurrences (all)	3	2	0
Pruritus			
subjects affected / exposed	4 / 23 (17.39%)	13 / 67 (19.40%)	1 / 12 (8.33%)
occurrences (all)	5	16	1
Rash			
subjects affected / exposed	0 / 23 (0.00%)	16 / 67 (23.88%)	3 / 12 (25.00%)
occurrences (all)	0	19	4
Rash maculo-papular			
subjects affected / exposed	4 / 23 (17.39%)	14 / 67 (20.90%)	1 / 12 (8.33%)
occurrences (all)	5	22	1
Vitiligo			
subjects affected / exposed	3 / 23 (13.04%)	6 / 67 (8.96%)	0 / 12 (0.00%)
occurrences (all)	3	6	0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 23 (4.35%)	6 / 67 (8.96%)	0 / 12 (0.00%)
occurrences (all)	1	12	0
Haematuria			
subjects affected / exposed	0 / 23 (0.00%)	5 / 67 (7.46%)	1 / 12 (8.33%)
occurrences (all)	0	5	1
Oliguria			
subjects affected / exposed	0 / 23 (0.00%)	3 / 67 (4.48%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 23 (8.70%)	0 / 67 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 23 (8.70%)	6 / 67 (8.96%)	2 / 12 (16.67%)
occurrences (all)	2	8	2
Back pain			
subjects affected / exposed	1 / 23 (4.35%)	9 / 67 (13.43%)	2 / 12 (16.67%)
occurrences (all)	1	11	2
Bone pain			
subjects affected / exposed	2 / 23 (8.70%)	2 / 67 (2.99%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Groin pain			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 23 (0.00%)	5 / 67 (7.46%)	0 / 12 (0.00%)
occurrences (all)	0	6	0
Muscular weakness			
subjects affected / exposed	3 / 23 (13.04%)	3 / 67 (4.48%)	1 / 12 (8.33%)
occurrences (all)	3	3	1
Myalgia			
subjects affected / exposed	2 / 23 (8.70%)	5 / 67 (7.46%)	0 / 12 (0.00%)
occurrences (all)	2	5	0
Pain in extremity			

subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Klebsiella infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 67 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 23 (30.43%)	19 / 67 (28.36%)	2 / 12 (16.67%)
occurrences (all)	8	22	2
Dehydration			
subjects affected / exposed	6 / 23 (26.09%)	5 / 67 (7.46%)	0 / 12 (0.00%)
occurrences (all)	6	5	0
Hyperglycaemia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 67 (2.99%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Hypoalbuminaemia			
subjects affected / exposed	7 / 23 (30.43%)	14 / 67 (20.90%)	0 / 12 (0.00%)
occurrences (all)	22	31	0
Hypocalcaemia			
subjects affected / exposed	4 / 23 (17.39%)	16 / 67 (23.88%)	1 / 12 (8.33%)
occurrences (all)	8	27	5
Hypokalaemia			
subjects affected / exposed	5 / 23 (21.74%)	17 / 67 (25.37%)	3 / 12 (25.00%)
occurrences (all)	8	30	6
Hypomagnesaemia			
subjects affected / exposed	1 / 23 (4.35%)	16 / 67 (23.88%)	4 / 12 (33.33%)
occurrences (all)	3	19	5
Hyponatraemia			
subjects affected / exposed	5 / 23 (21.74%)	11 / 67 (16.42%)	2 / 12 (16.67%)
occurrences (all)	6	17	3
Hypophosphataemia			
subjects affected / exposed	6 / 23 (26.09%)	30 / 67 (44.78%)	5 / 12 (41.67%)
occurrences (all)	12	74	7

Non-serious adverse events	Cohort 4		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	89 / 89 (100.00%)		
Vascular disorders			
Capillary leak syndrome subjects affected / exposed occurrences (all)	10 / 89 (11.24%) 13		
Flushing subjects affected / exposed occurrences (all)	4 / 89 (4.49%) 4		
Hypertension subjects affected / exposed occurrences (all)	17 / 89 (19.10%) 27		
Hypotension subjects affected / exposed occurrences (all)	27 / 89 (30.34%) 38		
Thrombophlebitis subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1		
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 16		
Chills subjects affected / exposed occurrences (all)	64 / 89 (71.91%) 76		
Fatigue subjects affected / exposed occurrences (all)	25 / 89 (28.09%) 30		
Malaise subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5		
Mucosal inflammation subjects affected / exposed occurrences (all)	4 / 89 (4.49%) 4		
Non-cardiac chest pain			

subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Oedema			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	8		
Oedema peripheral			
subjects affected / exposed	15 / 89 (16.85%)		
occurrences (all)	19		
Pain			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	42 / 89 (47.19%)		
occurrences (all)	78		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Hypersensitivity			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 89 (13.48%)		
occurrences (all)	13		
Dyspnoea			
subjects affected / exposed	15 / 89 (16.85%)		
occurrences (all)	16		
Epistaxis			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Hypoxia			
subjects affected / exposed	18 / 89 (20.22%)		
occurrences (all)	21		
Lung disorder			

subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	3		
Pleural effusion			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	8		
Pleuritic pain			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Pulmonary oedema			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	9		
Respiratory distress			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Tachypnoea			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	11		
Wheezing			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	8		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	9		
Confusional state			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		

Delirium			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	6		
Insomnia			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	7		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	19		
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	23		
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	16		
Blood bilirubin increased			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	12		
Blood creatine phosphokinase increased			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	8		
Blood creatinine increased			
subjects affected / exposed	9 / 89 (10.11%)		
occurrences (all)	10		
Breath sounds abnormal			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	12		
International normalised ratio increased			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		

Urine output decreased			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	10		
Weight increased			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	20		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Infusion related reaction			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
Skin laceration			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Atrial fibrillation			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Sinus tachycardia			
subjects affected / exposed	13 / 89 (14.61%)		
occurrences (all)	16		
Stress cardiomyopathy			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Tachycardia			

subjects affected / exposed	22 / 89 (24.72%)		
occurrences (all)	23		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	12 / 89 (13.48%)		
occurrences (all)	14		
Lethargy			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Presyncope			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	54 / 89 (60.67%)		
occurrences (all)	148		
Febrile neutropenia			
subjects affected / exposed	27 / 89 (30.34%)		
occurrences (all)	27		
Leukopenia			
subjects affected / exposed	29 / 89 (32.58%)		
occurrences (all)	49		
Lymphopenia			
subjects affected / exposed	28 / 89 (31.46%)		
occurrences (all)	59		
Neutropenia			
subjects affected / exposed	30 / 89 (33.71%)		
occurrences (all)	44		
Normocytic anaemia			

subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	9		
Pancytopenia			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Thrombocytopenia			
subjects affected / exposed	72 / 89 (80.90%)		
occurrences (all)	223		
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Eye disorders			
Uveitis			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	7 / 89 (7.87%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	29 / 89 (32.58%)		
occurrences (all)	36		
Dry mouth			

subjects affected / exposed	8 / 89 (8.99%)		
occurrences (all)	10		
Dyspepsia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	21 / 89 (23.60%)		
occurrences (all)	27		
Stomatitis			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	20 / 89 (22.47%)		
occurrences (all)	30		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	19 / 89 (21.35%)		
occurrences (all)	20		
Dry skin			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Petechiae			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	11 / 89 (12.36%)		
occurrences (all)	12		
Rash			
subjects affected / exposed	23 / 89 (25.84%)		
occurrences (all)	33		
Rash maculo-papular			
subjects affected / exposed	10 / 89 (11.24%)		
occurrences (all)	13		

Vitiligo subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Haematuria subjects affected / exposed occurrences (all) Oliguria subjects affected / exposed occurrences (all)	 9 / 89 (10.11%) 16 4 / 89 (4.49%) 4 5 / 89 (5.62%) 5		
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all)	 1 / 89 (1.12%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Groin pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all)	 3 / 89 (3.37%) 3 7 / 89 (7.87%) 9 0 / 89 (0.00%) 0 0 / 89 (0.00%) 0 3 / 89 (3.37%) 3 3 / 89 (3.37%) 3		

Myalgia subjects affected / exposed occurrences (all)	2 / 89 (2.25%) 2		
Pain in extremity subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 8		
Infections and infestations Klebsiella infection subjects affected / exposed occurrences (all)	0 / 89 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	11 / 89 (12.36%) 12		
Dehydration subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1		
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 5		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 25		
Hypocalcaemia subjects affected / exposed occurrences (all)	13 / 89 (14.61%) 33		
Hypokalaemia subjects affected / exposed occurrences (all)	26 / 89 (29.21%) 47		
Hypomagnesaemia subjects affected / exposed occurrences (all)	15 / 89 (16.85%) 21		
Hyponatraemia subjects affected / exposed occurrences (all)	8 / 89 (8.99%) 14		
Hypophosphataemia			

subjects affected / exposed occurrences (all)	28 / 89 (31.46%) 57		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2015	Updated text from "The final cell product will be formulated after harvesting and washing in 500 mL of a 1:1 (v/v) solution of HypoThermosol™ and Plasma-Lyte A™ containing 1% HSA (compatible for human infusion)." To "The final cell product is formulated in a minimum of 50% HypoThermosol™ in Plasma-Lyte A™ (volume/volume) and up to 1% HSA (compatible for human infusion) containing 300 IU/mL IL2. The final product will be available for administration in one of two volumes for infusion: 1) 250 mL (in a 300-mL capacity infusion bag) when the total TIL harvested are ≤ 75x10^9 OR 2)500 mL (in a 600-mL capacity infusion bag) when the total TIL harvested are >75 x 10^9. The cell concentration range is 5.5 x 10^6 to 300 x 10^6/mL in the final product, with a dose range of 1.5 to 150 x 10^9 total viable cells. " Changed "Lonza" to "Central TIL Manufacturing Facility". Chest CT - language added to include neck imaging. Added clarifying information that eye exam is a Slit Lamp Eye exam. Previously stated, "The sample size is driven by the need to obtain 20 eligible patients. An eligible patient is one that meets all screening criteria, has been resected for TIL preparation and successfully infused treatment. Complete treatment is defined as successful infusion with LN-144 followed by IL-2". This has been changed to, "The sample size is driven by the need to obtain 20 patients who complete treatment. Complete treatment is defined as successful infusion with LN-144 followed by IL-2". Updated cardiac test text to the following "Cardiac evaluation (stress thallium) for all patients. Echocardiogram/ or MUGA if patient is ≥ 60 years of age or older; patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias. Stress thallium must show normal LVEF and unimpaired wall movement". Changed age from "18- 70, inclusive" to "Greater than 18". ...
18 July 2016	Additional objective added. Study design updated to reflect addition of TIL + durvalumab cohort. Change in sample size from 20 TIL alone patients to 15 TIL alone (Cohort 1) + 10 TIL & durvalumab (Cohort 2) patients. Clarified upper age limit: >65 with consultation with Medical Monitor & PI. Correct inclusion criterion regarding EBV testing. Allow palliative radiation during TIL manufacture period. Eased requirement for mandatory colonoscopy in patients with prior colitis. Eased requirement regarding brain metastases.
08 August 2016	CD4 count added back to the Schedule of Events table at the Day 28, Day 42, Day 84 and 6 Months visits
04 February 2017	The main purposes for revising the C-144-01 protocol are to: Addition of cohort of patients receiving LN-144 produced with a shortened process. Addition of cohort of patients harvested and treated a second time. Addition of an additional assessment time point. Addition of exploratory endpoint of HRQoL. Numerous clarifications to statistical section and minor operational changes addressing operational issues. Numerous typographical changes were made for clarity and consistency.

13 May 2017	The major changes and purposes for revising the C-144-01 protocol are to: Update of Primary and Secondary Objectives and Endpoints. Clarification of Exploratory Objectives and Endpoints. Adjustment of Eligibility Criteria for definition of Patient Population. Adjustment of Sample Size and rationale for determination. Clarification around requirements for Cohort 3 patients. Clarification around assessment and procedure timing. Numerous clarifications to Safety and Statistical sections. Updating of key Sponsor and designee contact information
23 March 2018	Number of clinical sites and sample size of patients per cohort were updated. Dose and treatment schedule revised in Synopsis and Protocol body to clarify changes to IL-2 administration, delineate between noncryopreserved product (Gen 1 [Cohort 1]), cryopreserved product (Gen 2 [Cohort 2]), and Cohort 3 [Gen 2] retreatment cohort, including Sponsor decision to close enrollment in Cohort 1. Inclusion criteria revised to clarify requirement for surgical resection of lesion, approved methods of birth control (ie, true sexual abstinence) and duration of contraception use, washout for prior anticancer therapies (targeted therapies, chemotherapies, immunotherapy, and palliative radiation) and specify that patients must have no other treatment options. Exclusion criteria revised to clarify exclusion of patients have received an organ allograph or those with specific conditions, such as active systemic infection, (eg, syphilis infection) or others, addition of exclusion for patients with a history of hypersensitivity reaction for aminoglycoside antibiotics, components of TIL product; requirements for echocardiogram and multiple gated acquisition scan at Screening, and cardia stress testing for assessment per NYHA functional classification related to atrial and/or ventricular arrhythmias, left ventricular ejection fraction, and wall movement abnormalities; exclusion window for live or attenuated vaccines; exclusion of patients who require immediate attention or would be at a disadvantage in participating and those who are protected or otherwise unable to provide proper consent. Treatment Cohorts more clearly delineated as first generation (Gen 1 infusion product [for Cohort 1]), second generation (Gen 2 infusion product [for Cohort 2]), and retreatment cohort for second TIL therapy (Cohort 3), including sponsor decision to close Cohort 1; and further to have all newly enrolled patients in Cohort 3 receive Gen 2 LN-144 infusion product.
20 December 2018	The main purpose of the amendment is to add a confirmatory and pivotal cohort, Cohort 4, to allow additional enrollment of approximately 75 patients to further investigate the efficacy and safety of LN-144. The sample size is based on a response rate of 4–10% to chemotherapy given second line in Phase 3 studies of PD-1 blocking antibodies. The Primary Endpoint of ORR assessment has been upgraded from Investigator assessment to an Independent Review Committee (IRC) per the FDA’s recommendation for a study intended to support product registration. The inclusion criteria for the study have been updated to clarify eligibility: Patients with unresectable or metastatic melanoma who have previously been treated with at least one systemic therapy including a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor. Updated the Statistical and Analytical Plans to reflect current status and future analysis of all cohorts. There will be a blinded independent review (BIRC) implemented to review the efficacy data in Cohort 4. Confirmatory scans will be performed at least 4 weeks after initial response is documented for partial responders and complete responders per RECIST v1.1. irRECIST was part of Cohort 1 and Cohort 2 as assessed by an IRC and will now be assessed by the Investigator for Cohort 4 patients as an exploratory endpoint. Cohort 1 is now closed to Screening and enrollment, and patients who remain on study are in OS Follow-up. Cohort 2 is closed to enrollment, but a few patients were being screened at the time of the study closing for enrollment, therefore these patients will still be enrolled and/or treated. Cohort 3 remains open to enrollment for up to 10 patients who previously received treatment under Cohort 1, Cohort 2, or Cohort 4.

22 October 2019	Incorporation of the product release specification for total viable cells and clarification that patients will receive the full dose of product manufactured and released. Addition of the Independent Data Monitoring Committee (IDMC). Clarification of the Data Safety Monitoring Board (DSMB) responsibility for Cohort 3. Clarification on the interim analysis. Changes/clarification of study procedures, including hospitalization requirement, acceptable laboratory tests for viral infection and coagulation, and dosing calculation of chemotherapy using body weight. Change of baseline brain MRI window from 3 weeks to 4 weeks prior to Day 0, to minimize unnecessary scan if not clinically indicated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36600653

http://www.ncbi.nlm.nih.gov/pubmed/40454684

http://www.ncbi.nlm.nih.gov/pubmed/40693376