Clinical trial results:
A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3high Small Cell Lung Cancer (SCLC) who have First Disease Progression During or Following Front-Line Platinum-Based Chemotherapy (TAHOE)

Summary

EudraCT number	2016-003726-17
Trial protocol	DK SE PT GB CZ DE HU BE LV NL GR BG PL FR ES HR IT RO
Global end of trial date	12 February 2020

Results information

Result version number	v2 (current)
This version publication date	12 March 2021
First version publication date	14 February 2021
Version creation reason	• Correction of full data set correction to time frame of AEs

Trial information

Trial identification

Sponsor protocol code	M16-289

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03061812
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road,, Maidenhead, Berkshire, United Kingdom, SL6 4UB
Public contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 8006339110, abbvieclinicaltrials@abbvie.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	12 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study are to assess if treatment with rovalpituzumab tesirine improves overall survival (OS) compared to topotecan in subjects with advanced or metastatic delta-like protein 3 high (DLL3high) SCLC who have first disease progression during or following frontline platinum based chemotherapy.

Protection of trial subjects:

Subject and/or legal guardian read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Belarus: 1
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	Ukraine: 9
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 17

Country: Number of subjects enrolled	Greece: 22
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 25
Worldwide total number of subjects	444
EEA total number of subjects	221

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)	245
From 65 to 84 years	196
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The collection of tumor material for DLL3 testing was done at any time after the informed consent is signed and prior to randomization. Screening procedures and radiographic assessments (computed tomography scan or magnetic resonance imaging) were performed within 28 days prior to randomization.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Topotecan

Arm description:

Topotecan given as an intravenous (IV) infusion over 30 minutes at a dose of 1.5 mg/m^2 on Days 1 to 5 of each 21-day cycle.

Arm type	Active comparator
Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Topotecan was given as an IV infusion over 30 minutes at a dose of 1.5 mg/m^2 on Days 1 to 5 of 21-day cycle.

Arm title	Rovalpituzumab Tesirine

Arm description:

Rovalpituzumab tesirine IV administration (dosing based on actual body weight) on Day 1 of a 42-day cycle for 2 cycles, with up to 2 additional cycles permitted.

Dexamethasone coadministered orally (PO) twice daily at a dose of 8 mg on Day -1, Day 1, and Day 2 of each 42-day cycle in which rovalpituzumab tesirine is administered.

Arm type	Experimental
Investigational medicinal product name	Rovalpituzumab tesirine
Investigational medicinal product code	
Other name	Rova-T
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rovalpituzumab tesirine will be given by IV infusion over approximately 30 minutes (window 20 – 45 minutes), adjusted to participant tolerability, at a dose of 0.3 mg/kg on Day 1 of a 42-Day cycle for 2 cycles.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dexamethasone dosing occurred such that there were approximately 12-hours (i.e., 10 – 14 hours) between AM and PM doses. The first dose
of the dexamethasone on the day of dosing was at least 30 minutes but no more than 4 hours prior to the rovalpituzumab tesirine infusion.

Number of subjects in period 1	Topotecan	Rovalpituzumab Tesirine
Started	148	296
Completed	148	296

Baseline characteristics

Reporting groups	
Reporting group title	Topotecan
Reporting group description:	
Topotecan given as an intravenous (IV) infusion over 30 minutes at a dose of 1.5 mg/m^2 on Days 1 to 5 of each 21-day cycle.	
Reporting group title	Rovalpituzumab Tesirine
Reporting group description:	
Rovalpituzumab tesirine IV administration (dosing based on actual body weight) on Day 1 of a 42-day cycle for 2 cycles, with up to 2 additional cycles permitted. Dexamethasone coadministered orally (PO) twice daily at a dose of 8 mg on Day -1, Day 1, and Day 2 of each 42-day cycle in which rovalpituzumab tesirine is administered.	

Reporting group values	Topotecan	Rovalpituzumab Tesirine	Total
Number of subjects	148	296	444
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	63.4	63.0	
standard deviation	± 8.72	± 8.57	-
Gender categorical			
Units: Subjects			
Female	62	105	167
Male	86	191	277
Race			
Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	23	57	80
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	2	0	2
White	122	236	358
More than one race	0	2	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	9	11
Not Hispanic or Latino	146	287	433

End points

End points reporting groups

Reporting group title	Topotecan

Reporting group description:

Topotecan given as an intravenous (IV) infusion over 30 minutes at a dose of 1.5 mg/m^2 on Days 1 to 5 of each 21-day cycle.

Reporting group title	Rovalpituzumab Tesirine

Reporting group description:

Rovalpituzumab tesirine IV administration (dosing based on actual body weight) on Day 1 of a 42-day cycle for 2 cycles, with up to 2 additional cycles permitted.

Dexamethasone coadministered orally (PO) twice daily at a dose of 8 mg on Day -1, Day 1, and Day 2 of each 42-day cycle in which rovalpituzumab tesirine is administered.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from the date of randomization to the date of death from any cause. Participants were censored at the last date they were documented alive. After the End of treatment, survival information was collected at approximately 6-week intervals (or as requested by sponsor to support data analysis) continuing until the endpoint of death, the participant became lost to follow-up, AbbVie terminated the study, or until 12 February 2020. Calculated using the Kaplan-Meier product-limit method.

End point type	Primary

End point timeframe:

From randomization until the end of study; median time on follow-up was 20 and 20.6 months for the topotecan and rovalpituzumab tesirine arms, respectively.

End point values	Topotecan	Rovalpituzumab Tesirine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[1]	296[2]		
Units: months				
median (confidence interval 95%)	8.57 (7.69 to 10.12)	6.34 (5.55 to 7.33)		

Notes:

[1] - randomized participants

[2] - randomized participants

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio calculated using a Cox proportional hazards regression model, with treatment and randomization stratification factors as covariates.

Comparison groups	Topotecan v Rovalpituzumab Tesirine

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.82

Notes:

[3] - Two-sided p-value stratified by the randomization stratification factors.

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS is defined as the number of months from the date of randomization until the date of first progression or the date of a participant's death, whichever occurs first. If a participant neither experienced disease progression nor died, then the participant's data were censored at the last date of radiographic assessment that they were documented to be progression free. Calculated using the Kaplan-Meier product-limit method.

Radiographic tumor assessments for response were conducted by CT scanning according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Progressive Disease (PD) was defined as at least a 20% increase in the size of target lesions and an absolute increase of at least 5 mm taking as reference the smallest lesion size recorded since the treatment started (baseline or after), or the appearance of one or more new lesions.

End point type	Secondary

End point timeframe:

From randomization until the end of study; median time on follow-up was 20 and 20.6 months for the topotecan and rovalpituzumab tesirine arms, respectively.

End point values	Topotecan	Rovalpituzumab Tesirine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148[4]	296[5]		
Units: months				
median (confidence interval 95%)	4.27 (3.75 to 5.42)	3.02 (2.86 to 3.61)		

Notes:

[4] - randomized participants

[5] - randomized participants

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio calculated using a Cox proportional hazards regression model, with treatment and randomization stratification factors as covariates.

Comparison groups	Topotecan v Rovalpituzumab Tesirine

Number of subjects included in analysis	444
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	1.87

Notes:

[6] - Two-sided p-value stratified by the randomization stratification factors.

Secondary: Change From Baseline of the Physical Functioning Scale Score in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 15-Palliative Care (EORTC QLQ-C15-PAL) at Week 7

End point title	Change From Baseline of the Physical Functioning Scale Score in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 15-Palliative Care (EORTC QLQ-C15-PAL) at Week 7

End point description:

The EORTC QLQ-C15-PAL is an abbreviated 15-item version of the EORTC core quality of life questionnaire (EORTC QLQ-C30) developed for use in palliative care. The score of 'physical functioning scale' score ranges from 0 (very poor) to 100 (excellent).

End point type	Secondary

End point timeframe:

Baseline, Week 7

End point values	Topotecan	Rovalpituzumab Tesirine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[7]	217[8]		
Units: score on a scale				
least squares mean (confidence interval 95%)	-7.16 (-11.95 to -2.36)	-7.66 (-11.31 to -4.01)		

Notes:

[7] - Randomized participants with an assessment at baseline and Week 7.

[8] - Randomized participants with an assessment at baseline and Week 7.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Topotecan v Rovalpituzumab Tesirine

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean of Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.66
upper limit	4.65
Variability estimate	Standard error of the mean
Dispersion value	2.62

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants whose best overall response is either complete response (CR) or partial response (PR) according to RECIST version 1.1. Radiographic tumor assessments for response were conducted by CT scanning, and assessed from the date of randomization until disease progression or death, whichever came first. Any participant who did not meet CR or PR, including those who did not have post-baseline radiological assessments were considered non-responders.

CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

Radiographic tumor assessments were conducted at baseline, every 6 weeks for 30 weeks, then every 9 weeks until progression or death; median time on follow-up was 20 and 20.6 months for the topotecan and rovalpituzumab tesirine arms, respectively.

End point values	Topotecan	Rovalpituzumab Tesirine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129[9]	287[10]		
Units: percentage of participants				
number (confidence interval 95%)	20.9 (14.27 to 28.97)	14.6 (10.75 to 19.26)		

Notes:

[9] - Randomized participants with measurable disease at baseline.

[10] - Randomized participants with measurable disease at baseline.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Topotecan v Rovalpituzumab Tesirine

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3352 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.18

Notes:

[11] - Stratified by the randomization stratification factors.

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR is defined as percentage of participants whose best overall response is CR, PR, or stable disease (SD) according to RECIST version 1.1. Radiographic tumor assessments for response were conducted by CT scanning, and assessed from the date of randomization until disease progression or death, whichever came first. Any participant who did not meet CR, PR, or SD, including those who did not have post-baseline radiological assessments were considered as experiencing no clinical benefit.

CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

End point type	Secondary

End point timeframe:

Radiographic tumor assessments were conducted at baseline, every 6 weeks for 30 weeks, then every 9 weeks until progression or death; median time on follow-up was 20 and 20.6 months for the topotecan and rovalpituzumab tesirine arms, respectively.

End point values	Topotecan	Rovalpituzumab Tesirine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129[12]	287[13]		
Units: percentage of participants				
number (confidence interval 95%)	43.4 (34.71 to 52.42)	35.9 (30.34 to 41.74)		

Notes:

[12] - Randomized participants with measurable disease at baseline.

[13] - Randomized participants with measurable disease at baseline.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Topotecan v Rovalpituzumab Tesirine

Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0358 [14]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.12

Notes:

[14] - Stratified by the randomization stratification factors.

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR)

End point description:

DOR is defined as the time between the date of first response (CR or PR, whichever is recorded first) to the date of the first documented tumor progression (per RECIST version 1.1) or death due to any cause, whichever comes first. Radiographic tumor assessments for response were conducted by CT scanning, and assessed from the date of randomization until disease progression or death, whichever came first. Any participant who did not meet CR or PR, including those who did not have post-baseline radiological assessments were considered non-responders.

CR: Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary

End point timeframe:

Radiographic tumor assessments were conducted at baseline, every 6 weeks for 30 weeks, then every 9 weeks until progression or death; median time on follow-up was 20 and 20.6 months for the topotecan and rovalpituzumab tesirine arms, respectively.

End point values	Topotecan	Rovalpituzumab Tesirine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[15]	42[16]		
Units: months				
number (confidence interval 95%)	4.86 (3.94 to 7.85)	3.52 (2.76 to 4.17)		

Notes:

[15] - Randomized participants with measurable disease at baseline, and a response.

[16] - Randomized participants with measurable disease at baseline, and a response.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs and SAEs were collected from first dose of study drug until 70 days after the last dose of study drug; mean duration on study drug was 14.8 weeks and 11.3 weeks for the topotecan and rovalpituzumab tesirine arms, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Topotecan

Reporting group description:

Topotecan given as an intravenous (IV) infusion over 30 minutes at a dose of 1.5 mg/m^2 on Days 1 to 5 of each 21-day cycle.

Reporting group title	Rovalpituzumab Tesirine

Reporting group description:

Rovalpituzumab tesirine IV administration (dosing based on actual body weight) on Day 1 of a 42-day cycle for 2 cycles, with up to 2 additional cycles permitted.

Dexamethasone coadministered orally (PO) twice daily at a dose of 8 mg on Day -1, Day 1, and Day 2 of each 42-day cycle in which rovalpituzumab tesirine is administered.

Serious adverse events	Topotecan	Rovalpituzumab Tesirine	
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 129 (57.36%)	160 / 287 (55.75%)	
number of deaths (all causes)	104	254	
number of deaths resulting from adverse events	28	64	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CANCER PAIN			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL NEOPLASM			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED NEOPLASM			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG NEOPLASM			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MALIGNANT NEOPLASM OF SPINAL CORD			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	17 / 129 (13.18%)	30 / 287 (10.45%)	
occurrences causally related to treatment / all	0 / 19	0 / 32	
deaths causally related to treatment / all	0 / 17	0 / 26	
METASTASES TO MENINGES			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEOPLASM MALIGNANT			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NEOPLASM PROGRESSION			
subjects affected / exposed	2 / 129 (1.55%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
NON-SMALL CELL LUNG CANCER			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SMALL CELL LUNG CANCER			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
SMALL CELL LUNG CANCER METASTATIC			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR NECROSIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR PAIN			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	0 / 129 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SHOCK HAEMORRHAGIC			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
SUPERIOR VENA CAVA SYNDROME			

subjects affected / exposed	1 / 129 (0.78%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
CHEST PAIN			
subjects affected / exposed	2 / 129 (1.55%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
DISEASE PROGRESSION			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
FACE OEDEMA			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	0 / 129 (0.00%)	6 / 287 (2.09%)	
occurrences causally related to treatment / all	0 / 0	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	6 / 129 (4.65%)	8 / 287 (2.79%)	
occurrences causally related to treatment / all	1 / 7	1 / 10	
deaths causally related to treatment / all	0 / 3	0 / 6	
MALAISE			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTIPLE ORGAN DYSFUNCTION SYNDROME			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POLYSEROSITIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	3 / 129 (2.33%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEROSITIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
ANAPHYLACTIC REACTION			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

ACUTE LUNG INJURY			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHMA			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
ATELECTASIS			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	0 / 129 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC RESPIRATORY FAILURE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	0 / 129 (0.00%)	16 / 287 (5.57%)	
occurrences causally related to treatment / all	0 / 0	5 / 20	
deaths causally related to treatment / all	0 / 0	0 / 1	
DYSPNOEA AT REST			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPTYSIS			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	2 / 129 (1.55%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 129 (0.00%)	17 / 287 (5.92%)	
occurrences causally related to treatment / all	0 / 0	13 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURISY			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	1 / 129 (0.78%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			

subjects affected / exposed	0 / 129 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY FIBROSIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY DISTRESS			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 129 (0.78%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	2 / 129 (1.55%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CULTURE URINE POSITIVE			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL CONDITION ABNORMAL			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
LIPASE INCREASED			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EYELID CONTUSION			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

FALL			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEAT STROKE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THERMAL BURN			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
APLASIA			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARRHYTHMIA			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
CARDIAC FAILURE			
subjects affected / exposed	0 / 129 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC TAMPONADE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
ATAXIA			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVICAL CORD COMPRESSION			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSED LEVEL OF			

CONSCIOUSNESS			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLIC STROKE			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERALISED TONIC-CLONIC SEIZURE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	2 / 129 (1.55%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRACRANIAL PRESSURE INCREASED			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
INTRAVENTRICULAR HAEMORRHAGE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MEMORY IMPAIRMENT			

subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOMNOLENCE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 129 (3.10%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	4 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	11 / 129 (8.53%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	12 / 13	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
HAEMATOTOXICITY			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			

subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	6 / 129 (4.65%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	2 / 129 (1.55%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	10 / 129 (7.75%)	5 / 287 (1.74%)	
occurrences causally related to treatment / all	10 / 10	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 129 (0.78%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN LOWER			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 129 (0.00%)	4 / 287 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	0 / 129 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC HAEMORRHAGE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE PERFORATION			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 129 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBILEUS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLANGITIS			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLESTASIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
JAUNDICE CHOLESTATIC			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
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			
ERYTHEMA			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
ADRENAL INSUFFICIENCY			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			

subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOPOROSIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCESS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL PNEUMONIA			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
BRONCHITIS			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANDIDA INFECTION			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			

subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	2 / 129 (1.55%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 129 (0.00%)	5 / 287 (1.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG ABSCESS			
subjects affected / exposed	1 / 129 (0.78%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORCHITIS			

subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITONITIS			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	6 / 129 (4.65%)	19 / 287 (6.62%)	
occurrences causally related to treatment / all	3 / 6	4 / 26	
deaths causally related to treatment / all	0 / 0	2 / 7	
PNEUMONIA NECROTISING			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA STAPHYLOCOCCAL			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 129 (0.00%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SALMONELLOSIS			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 129 (1.55%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	0 / 129 (0.00%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DECREASED APPETITE			
subjects affected / exposed	1 / 129 (0.78%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 129 (0.78%)	2 / 287 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			

subjects affected / exposed	0 / 129 (0.00%)	1 / 287 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 129 (0.78%)	0 / 287 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	3 / 129 (2.33%)	3 / 287 (1.05%)	
occurrences causally related to treatment / all	0 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Topotecan	Rovalpituzumab Tesirine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 129 (91.47%)	245 / 287 (85.37%)	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	4 / 129 (3.10%)	16 / 287 (5.57%)	
occurrences (all)	6	16	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	21 / 129 (16.28%)	36 / 287 (12.54%)	
occurrences (all)	28	47	
CHEST PAIN			
subjects affected / exposed	4 / 129 (3.10%)	18 / 287 (6.27%)	
occurrences (all)	4	19	
FATIGUE			
subjects affected / exposed	35 / 129 (27.13%)	65 / 287 (22.65%)	
occurrences (all)	47	85	
OEDEMA PERIPHERAL			
subjects affected / exposed	11 / 129 (8.53%)	51 / 287 (17.77%)	
occurrences (all)	14	58	
PYREXIA			

subjects affected / exposed	6 / 129 (4.65%)	16 / 287 (5.57%)	
occurrences (all)	9	18	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	16 / 129 (12.40%)	42 / 287 (14.63%)	
occurrences (all)	19	45	
DYSPNOEA			
subjects affected / exposed	25 / 129 (19.38%)	56 / 287 (19.51%)	
occurrences (all)	28	69	
EPISTAXIS			
subjects affected / exposed	14 / 129 (10.85%)	9 / 287 (3.14%)	
occurrences (all)	16	11	
PLEURAL EFFUSION			
subjects affected / exposed	5 / 129 (3.88%)	65 / 287 (22.65%)	
occurrences (all)	6	72	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	9 / 129 (6.98%)	15 / 287 (5.23%)	
occurrences (all)	9	17	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 129 (0.78%)	18 / 287 (6.27%)	
occurrences (all)	3	31	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	3 / 129 (2.33%)	20 / 287 (6.97%)	
occurrences (all)	4	34	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	12 / 129 (9.30%)	1 / 287 (0.35%)	
occurrences (all)	20	1	
PLATELET COUNT DECREASED			
subjects affected / exposed	7 / 129 (5.43%)	9 / 287 (3.14%)	
occurrences (all)	13	11	
WEIGHT DECREASED			
subjects affected / exposed	7 / 129 (5.43%)	18 / 287 (6.27%)	
occurrences (all)	7	22	

Cardiac disorders			
PERICARDIAL EFFUSION			
subjects affected / exposed	3 / 129 (2.33%)	56 / 287 (19.51%)	
occurrences (all)	3	58	
Nervous system disorders			
DYSGEUSIA			
subjects affected / exposed	7 / 129 (5.43%)	6 / 287 (2.09%)	
occurrences (all)	8	6	
HEADACHE			
subjects affected / exposed	11 / 129 (8.53%)	20 / 287 (6.97%)	
occurrences (all)	14	21	
PARAESTHESIA			
subjects affected / exposed	7 / 129 (5.43%)	0 / 287 (0.00%)	
occurrences (all)	7	0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	75 / 129 (58.14%)	42 / 287 (14.63%)	
occurrences (all)	136	53	
LEUKOPENIA			
subjects affected / exposed	25 / 129 (19.38%)	4 / 287 (1.39%)	
occurrences (all)	80	8	
NEUTROPENIA			
subjects affected / exposed	50 / 129 (38.76%)	14 / 287 (4.88%)	
occurrences (all)	136	20	
THROMBOCYTOPENIA			
subjects affected / exposed	45 / 129 (34.88%)	39 / 287 (13.59%)	
occurrences (all)	94	75	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	11 / 129 (8.53%)	21 / 287 (7.32%)	
occurrences (all)	11	25	
CONSTIPATION			
subjects affected / exposed	29 / 129 (22.48%)	33 / 287 (11.50%)	
occurrences (all)	36	35	
DIARRHOEA			
subjects affected / exposed	25 / 129 (19.38%)	20 / 287 (6.97%)	
occurrences (all)	29	24	

NAUSEA			
subjects affected / exposed	40 / 129 (31.01%)	65 / 287 (22.65%)	
occurrences (all)	58	77	
VOMITING			
subjects affected / exposed	17 / 129 (13.18%)	30 / 287 (10.45%)	
occurrences (all)	20	35	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	20 / 129 (15.50%)	3 / 287 (1.05%)	
occurrences (all)	24	3	
ERYTHEMA			
subjects affected / exposed	0 / 129 (0.00%)	16 / 287 (5.57%)	
occurrences (all)	0	22	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	0 / 129 (0.00%)	46 / 287 (16.03%)	
occurrences (all)	0	60	
RASH			
subjects affected / exposed	1 / 129 (0.78%)	25 / 287 (8.71%)	
occurrences (all)	1	34	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	10 / 129 (7.75%)	16 / 287 (5.57%)	
occurrences (all)	11	19	
BACK PAIN			
subjects affected / exposed	12 / 129 (9.30%)	21 / 287 (7.32%)	
occurrences (all)	12	22	
MYALGIA			
subjects affected / exposed	7 / 129 (5.43%)	7 / 287 (2.44%)	
occurrences (all)	7	8	
Infections and infestations			
URINARY TRACT INFECTION			
subjects affected / exposed	8 / 129 (6.20%)	13 / 287 (4.53%)	
occurrences (all)	11	13	
Metabolism and nutrition disorders			
DECREASED APPETITE			

subjects affected / exposed	35 / 129 (27.13%)	71 / 287 (24.74%)	
occurrences (all)	47	87	
HYPOALBUMINAEMIA			
subjects affected / exposed	3 / 129 (2.33%)	17 / 287 (5.92%)	
occurrences (all)	3	18	
HYPOKALAEMIA			
subjects affected / exposed	13 / 129 (10.08%)	18 / 287 (6.27%)	
occurrences (all)	13	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2017	Specified that DLL3high is defined as ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay, provided additional detail for definitive treatment for CNS disease and include subjects with stable or improved clinical status prior to randomization, provided modified exclusion windows for prior history of effusions, clarified that the corticosteroid exclusion criterion is to exclude subjects with unstable CNS metastases.
19 May 2017	Revised the exclusion criteria to provide additional safety parameters, clarified any prior exposure to a pyrrolobenzodiazepine- or indolinobenzodiazepine-based drug is excluded, added new criterion since the antibody is produced using these cells and there could be possible cross-reactivity in the product.
02 July 2018	Removed requirement for prospective CRAC confirmation for disease measurability to simplify patient randomization logistics and due to change of objective response rate (ORR) from primary to secondary endpoint, clarify definition of non-active CNS metastases and requirements for study entry for subjects with history of CNS metastases with complete response, added more stringent safety requirements and allowances for flexibility on dose interruptions if treatment benefits were observed, updated dose reduction guidelines incorporating information on rovalpituzumab tesirine tolerability available to date.
08 January 2019	Following the 4th safety review by the IDMC on 03 December 2018, the IDMC recommended that enrollment in the study be discontinued due to shorter OS in the rovalpituzumab tesirine arm compared with the topotecan control arm. At this point in time, 444 subjects had enrolled of the planned enrollment for the study of 600 subjects. Amendment 4 discontinued CRAC assessment of response and progression; these analyses were conducted using investigator assessment. For patients that were currently on treatment with rovalpituzumab tesirine, the IDMC recommended that sites and patients make individual decisions as to whether or not to continue treatment based on patient level response. A series of changes were made to the protocol to reflect that no further formal statistical hypothesis testing related to efficacy endpoints would be conducted, and to clarify the study duration reflecting the end of treatment no later than 04 December 2019 and survival follow up no later than 12 February 2020.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported