Clinical trial results:
A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma

Summary

EudraCT number	2015-002469-41
Trial protocol	GB DE BE FR IT
Global end of trial date	26 February 2024

Results information

Result version number	v1 (current)
This version publication date	23 February 2025
First version publication date	23 February 2025

Trial information

Trial identification

Sponsor protocol code	EZH-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02601950
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Epizyme, Inc.
Sponsor organisation address	400 Technology Square, 4th Floor, Cambridge, United States, 02139
Public contact	Shefali Agarwal, MBBS, MPH, MIS, Epizyme, Inc., 001 855500-1011, clinicaltrials@epizyme.com
Scientific contact	Shefali Agarwal, MBBS, MPH, MIS, Epizyme, Inc., 001 855500-1011, clinicaltrials@epizyme.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-003055-PIP02-23
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	28 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the overall response rate (ORR) following oral administration of tazemetostat 800 milligrams (mg) twice daily (BID) in Cohort 1 (rhabdoid tumours), Cohort 3 (other integrase interactor 1 [INI-1]-negative tumours or any solid tumour with enhancer of zeste homologue-2 (EZH2) gain of function [GOF] mutation), Cohort 4 (renal medullary carcinoma [RMC]), Cohort 5 (epithelioid sarcoma [ES]), Cohort 6 (ES with optional tumour biopsy), and Cohort 7 (chordoma).

- To determine the progression-free survival (PFS) rate following 16 weeks of oral administration of tazemetostat 800 mg BID in Cohort 2 (relapsed/ refractory synovial sarcoma with SS18-SSX rearrangement).

- To assess the safety and tolerability of tazemetostat 1600 mg QD in Cohort 8 (ES treated with tazemetostat 1600 mg once daily [QD]).

Protection of trial subjects:

The procedures set out in the study protocol pertaining to the conduct, evaluation, and documentation of this study were designed to ensure that the sponsor and investigators are by Good Clinical Practice as described in the International Conference on Harmonisation Tripartite Guideline E6. Compliance with these regulations also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study was also carried out in keeping with local legal and regulatory requirements. Participant confidentiality was strictly held in trust by the sponsor and/or their designee(s), participating Investigators, and site staff.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2015
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: 7
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	United States: 150

Worldwide total number of subjects	267
EEA total number of subjects	71

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)	7
Adults (18-64 years)	247
From 65 to 84 years	11
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This Phase II, open-label study was conducted at 28 sites in 9 countries from 22 December 2015 to 26 February 2024.

Pre-assignment

Screening details:

Participants were enrolled into 1 of the 8 cohorts based on tumor type. A total of 267 participants were enrolled in the study.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Rhabdoid Tumors: Cohort 1

Arm description:

Participants with rhabdoid tumors (malignant rhabdoid tumor [MRT], rhabdoid tumors of the kidney [RTK], atypical teratoid rhabdoid tumor [ATRT], and selected tumors with rhabdoid features, including small cell carcinoma of the ovary hypercalcemic type [SCCOHT], also known as malignant rhabdoid tumor of the ovary [MRTO]) received tazemetostat 800 milligram (mg) twice daily (BID) orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 800 mg BID orally in continuous 28-day cycles.

Arm title	Synovial Sarcoma: Cohort 2

Arm description:

Participants with relapsed or refractory synovial sarcoma with SS18-SSX rearrangement received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 800 mg BID orally in continuous 28-day cycles.

Arm title	Other INI1-negative: Cohort 3

Arm description:

Participants with other INI-1-negative tumors or any solid tumor with EZH2 GOF mutation, including epithelioid malignant peripheral nerve sheath tumor (EMPNST), extraskeletal myxoid chondrosarcoma (EMC), myoepithelial carcinoma, other INI-1-negative malignant tumors with sponsor approval, any solid tumor with EZH2 GOF mutation including but not limited to Ewing's sarcoma and melanoma

received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 800 mg BID orally in continuous 28-day cycles.

Arm title	RMC: Cohort 4

Arm description:

Participants with RMC received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 800 mg BID orally in continuous 28-day cycles.

Arm title	ES: Cohort 5

Arm description:

Participants with ES received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 800 mg BID orally in continuous 28-day cycles.

Arm title	ES Paired Biopsy: Cohort 6

Arm description:

Participants with ES undergoing optional tumor biopsy received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 800 mg BID orally in continuous 28-day cycles.

Arm title	Chordoma: Cohort 7

Arm description:

Participants with poorly differentiated chordoma (or other chordoma with sponsor approval) received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of

an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 800 mg BID orally in continuous 28-day cycles.

Arm title	ES 1600 mg: Cohort 8

Arm description:

Participants with ES received tazemetostat 1600 mg once daily (QD) orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438
Other name	IPN60200
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received tazemetostat 1600 mg QD orally in continuous 28-day cycles.

Number of subjects in period 1	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3
Started	32	33	32
Completed	0	0	0
Not completed	32	33	32
Participant refused further study treatment	-	1	1
Disease progression - clinical	3	5	4
Adverse event (not related to study treatment)	1	-	-
Death	6	-	3
Unacceptable toxicity (related to study treatment)	-	-	-
Non-compliance	-	1	-
Disease progression - radiological	21	26	22
Unspecified	-	-	-
Investigator discretion	1	-	1
Participant enrolled in rollover study	-	-	1

Number of subjects in period 1	RMC: Cohort 4	ES: Cohort 5	ES Paired Biopsy: Cohort 6
Started	14	62	69
Completed	0	0	0
Not completed	14	62	69
Participant refused further study treatment	-	2	2

Disease progression - clinical	2	6	6
Adverse event (not related to study treatment)	-	-	2
Death	1	4	1
Unacceptable toxicity (related to study treatment)	-	-	1
Non-compliance	-	-	1
Disease progression - radiological	11	46	52
Unspecified	-	2	2
Investigator discretion	-	1	1
Participant enrolled in rollover study	-	1	1

Number of subjects in period 1	Chordoma: Cohort 7	ES 1600 mg: Cohort 8
Started	18	7
Completed	0	0
Not completed	18	7
Participant refused further study treatment	2	1
Disease progression - clinical	5	1
Adverse event (not related to study treatment)	-	-
Death	-	-
Unacceptable toxicity (related to study treatment)	-	-
Non-compliance	1	-
Disease progression - radiological	7	5
Unspecified	1	-
Investigator discretion	1	-
Participant enrolled in rollover study	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rhabdoid Tumors: Cohort 1
Reporting group description:	
Participants with rhabdoid tumors (malignant rhabdoid tumor [MRT], rhabdoid tumors of the kidney [RTK], atypical teratoid rhabdoid tumor [ATRT], and selected tumors with rhabdoid features, including small cell carcinoma of the ovary hypercalcemic type [SCCOHT], also known as malignant rhabdoid tumor of the ovary [MRTO]) received tazemetostat 800 milligram (mg) twice daily (BID) orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	
Reporting group title	Synovial Sarcoma: Cohort 2
Reporting group description:	
Participants with relapsed or refractory synovial sarcoma with SS18-SSX rearrangement received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	
Reporting group title	Other INI1-negative: Cohort 3
Reporting group description:	
Participants with other INI-1-negative tumors or any solid tumor with EZH2 GOF mutation, including epithelioid malignant peripheral nerve sheath tumor (EMPNST), extraskeletal myxoid chondrosarcoma (EMC), myoepithelial carcinoma, other INI-1-negative malignant tumors with sponsor approval, any solid tumor with EZH2 GOF mutation including but not limited to Ewing's sarcoma and melanoma received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	
Reporting group title	RMC: Cohort 4
Reporting group description:	
Participants with RMC received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	
Reporting group title	ES: Cohort 5
Reporting group description:	
Participants with ES received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	
Reporting group title	ES Paired Biopsy: Cohort 6
Reporting group description:	
Participants with ES undergoing optional tumor biopsy received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	
Reporting group title	Chordoma: Cohort 7
Reporting group description:	
Participants with poorly differentiated chordoma (or other chordoma with sponsor approval) received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	
Reporting group title	ES 1600 mg: Cohort 8
Reporting group description:	
Participants with ES received tazemetostat 1600 mg once daily (QD) orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group values	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3
Number of subjects	32	33	32
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	37.9	38.8	46.9
standard deviation	± 16.31	± 9.54	± 16.94
Gender categorical Units: Subjects			
Female	19	12	17
Male	13	21	15
Race Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	2	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	4	2
White	24	24	28
Unknown or Not Reported	2	5	1
More than one race	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	5	4
Not Hispanic or Latino	31	28	27
Unknown or Not Reported	1	0	1

Reporting group values	RMC: Cohort 4	ES: Cohort 5	ES Paired Biopsy: Cohort 6
Number of subjects	14	62	69
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	30.7	37.0	41.3
standard deviation	± 10.71	± 15.08	± 14.00
Gender categorical Units: Subjects			
Female	4	23	26
Male	10	39	43
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	7	9
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	11	4	1
White	2	47	54
Unknown or Not Reported	1	4	4
More than one race	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	7	4
Not Hispanic or Latino	13	53	55

Unknown or Not Reported	0	2	10

Reporting group values	Chordoma: Cohort 7	ES 1600 mg: Cohort 8	Total
Number of subjects	18	7	267
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	38.9	40.9	
standard deviation	± 17.49	± 15.74	-
Gender categorical Units: Subjects			
Female	8	4	113
Male	10	3	154
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	1	2	22
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	1	0	26
White	16	5	200
Unknown or Not Reported	0	0	17
More than one race	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	21
Not Hispanic or Latino	17	7	231
Unknown or Not Reported	1	0	15

End points

End points reporting groups

Reporting group title	Rhabdoid Tumors: Cohort 1
Reporting group description:	
Participants with rhabdoid tumors (malignant rhabdoid tumor [MRT], rhabdoid tumors of the kidney [RTK], atypical teratoid rhabdoid tumor [ATRT], and selected tumors with rhabdoid features, including small cell carcinoma of the ovary hypercalcemic type [SCCOHT], also known as malignant rhabdoid tumor of the ovary [MRTO]) received tazemetostat 800 milligram (mg) twice daily (BID) orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group title	Synovial Sarcoma: Cohort 2
Reporting group description:	
Participants with relapsed or refractory synovial sarcoma with SS18-SSX rearrangement received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group title	Other INI1-negative: Cohort 3
Reporting group description:	
Participants with other INI-1-negative tumors or any solid tumor with EZH2 GOF mutation, including epithelioid malignant peripheral nerve sheath tumor (EMPNST), extraskeletal myxoid chondrosarcoma (EMC), myoepithelial carcinoma, other INI-1-negative malignant tumors with sponsor approval, any solid tumor with EZH2 GOF mutation including but not limited to Ewing's sarcoma and melanoma received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group title	RMC: Cohort 4
Reporting group description:	
Participants with RMC received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group title	ES: Cohort 5
Reporting group description:	
Participants with ES received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group title	ES Paired Biopsy: Cohort 6
Reporting group description:	
Participants with ES undergoing optional tumor biopsy received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group title	Chordoma: Cohort 7
Reporting group description:	
Participants with poorly differentiated chordoma (or other chordoma with sponsor approval) received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Reporting group title	ES 1600 mg: Cohort 8
Reporting group description:	
Participants with ES received tazemetostat 1600 mg once daily (QD) orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.	

Primary: Cohorts 1, 3, 4, 5, 6 and 7: Objective response rate (ORR)

End point title	Cohorts 1, 3, 4, 5, 6 and 7: Objective response rate (ORR)[1][2]
End point description:	
ORR=percentage of participants who achieved a confirmed complete response (CR) or partial response (PR) based on the investigator review from start of treatment until progressive disease (PD) or start of	

subsequent anti-cancer therapy or cancer-related surgery, whichever was earlier, per response assessment in neuro-oncology (RANO) criteria for primary brain tumors or response evaluation criteria in solid tumors (RECIST) version(v) 1.1 criteria for all other solid tumors. CR=disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 millimeter (mm) in short axis. PR=at least 30% decrease in sum of diameters of target lesions, taking as a reference, baseline sum of diameters. PD=at least a 20% increase in sum of diameters of target lesions, taking as a reference, smallest sum of diameters recorded since treatment started. Sum must have an absolute increase from nadir of 5 mm. ITT population=all participants who received at least 1 dose of tazemetostat.

End point type	Primary

End point timeframe:

Tumor assessment performed at screening and every 8 weeks beginning at Cycle 3 Day 1, until disease progression or the start of subsequent anti-cancer therapy, whichever occurred first, up to 5.75 years (cycle duration: 28 days).

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: As the endpoint was descriptive in nature, no statistical analysis was reported.

[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 primary endpoint only applies to participants in Cohorts 1, 3, 4, 5, 6 and 7.

End point values	Rhabdoid Tumors: Cohort 1	Other INI1-negative: Cohort 3	RMC: Cohort 4	ES: Cohort 5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	32	14	62
Units: Percentage of participants				
number (confidence interval 95%)	9.4 (2.0 to 25.0)	9.4 (2.0 to 25.0)	0.0 (0.0 to 23.2)	16.1 (8.0 to 27.7)

End point values	ES Paired Biopsy: Cohort 6	Chordoma: Cohort 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	18		
Units: Percentage of participants				
number (confidence interval 95%)	15.9 (8.2 to 26.7)	5.6 (0.1 to 27.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Cohort 2: Progression-Free Survival (PFS) rate at 16 Weeks of Treatment With Tazemetostat

End point title	Cohort 2: Progression-Free Survival (PFS) rate at 16 Weeks of Treatment With Tazemetostat[3][4]

End point description:

PFS was defined as the interval of time between the date of the first dose of study treatment and the earliest date of PD or death due to any cause, whichever comes first, as per RECIST v 1.1 criteria. PFS rate at 16 week was estimated. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as a reference, smallest sum of diameters recorded since the treatment started. In addition, the sum must have an absolute increase from nadir of 5 mm. ITT population included all participants who received at least 1 dose of tazemetostat.

End point type	Primary

End point timeframe:

At 16 Weeks

Notes:

[3] - 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: As the endpoint was descriptive in nature, no statistical analysis was reported.

[4] - 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: Only participants in Cohort 2 were analyzed for this endpoint.

End point values	Synovial Sarcoma: Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: Percentage of participants				
number (confidence interval 95%)	15.2 (5.1 to 31.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Cohort 8: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Cohort 8: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)[5][6]

End point description:

An AE was defined as any untoward medical occurrence in a participant or clinical investigation participant administered a medicinal product and which did not necessarily have a causal relationship with this treatment. An SAE was defined as any untoward medical occurrence that, at any dose: resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect or was medically significant. TEAEs were defined as AEs if one of the following conditions met: emerged after the time of first dose administration, having been absent prior to the first dose; re-emerged, having been present but stopped prior to time of first dose administration; worsened in severity after the time of first dose administration relative to the pretreatment state, when the AE was continuous. Safety population=all participants in ITT population who had at least 1 post-dose safety observation recorded.

End point type	Primary

End point timeframe:

From first dose of study treatment (Day 1) up to 30 days after the last dose of study treatment, approximately 148 weeks

Notes:

[5] - 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: As the endpoint was descriptive in nature, no statistical analysis was reported.

[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: Only participants in Cohort 8 were analyzed for this endpoint.

End point values	ES 1600 mg: Cohort 8			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Participants				
TEAEs	7			
TESAEs	2			

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Duration of Response (DOR)

End point title	All Cohorts: Duration of Response (DOR)

End point description:

DOR was defined as time from the first documented evidence of CR or PR based on investigator review to the time of first documented PD or death due to any cause, whichever came first, as per RECIST v 1.1 criteria. CR was defined as disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 mm in the short axis. PR was defined as at least 30% decrease in sum of diameters of target lesions, taking as a reference, baseline sum of diameters. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as a reference, smallest sum of diameters recorded since the treatment started. In addition, the sum must have an absolute increase from nadir of 5 mm. ITT population included all participants who received at least 1 dose of tazemetostat. Only those participants with a confirmed CR or PR (responders) were analyzed.

End point type	Secondary

End point timeframe:

Tumor assessment performed at screening and every 8 weeks beginning at Cycle 3 Day 1, until disease progression or the start of subsequent anti-cancer therapy, whichever occurred first, up to 5.75 years (cycle duration 28 days)

End point values	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3	RMC: Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	0[7]	3	0[8]
Units: Weeks				
median (full range (min-max))	29.0 (24.1 to 32.1)	(to)	80.1 (24.1 to 87.6)	(to)

Notes:

[7] - None of the participants experienced a CR or PR.

[8] - None of the participants experienced a CR or PR.

End point values	ES: Cohort 5	ES Paired Biopsy: Cohort 6	Chordoma: Cohort 7	ES 1600 mg: Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	1	1
Units: Weeks				
median (full range (min-max))	88.0 (7.1 to 224.4)	96.1 (10.3 to 112.3)	151.6 (151.6 to 151.6)	119.4 (119.4 to 119.4)

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Progression-Free Survival (PFS)

End point title	All Cohorts: Progression-Free Survival (PFS)

End point description:

PFS was defined as the interval of time between the date of the first dose of study treatment and the earliest date of PD or death due to any cause, whichever comes first, as per RECIST v 1.1 criteria. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as a reference, smallest sum of diameters recorded since the treatment started. In addition, the sum must have an absolute increase from nadir of 5 mm. ITT population included all participants who received at least 1 dose of tazemetostat. Here, '99999' indicates that upper limit of confidence interval (CI) was not estimable due to insufficient number of participants with events at study closure.

End point type	Secondary

End point timeframe:

Tumor assessment performed at screening and every 8 weeks beginning at Cycle 3 Day 1, until disease progression or the start of subsequent anti-cancer therapy, whichever occurred first, up to 5.75 years (cycle duration 28 days)

End point values	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3	RMC: Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	32	14
Units: Weeks				
median (confidence interval 95%)	7.9 (7.7 to 15.1)	8.0 (7.6 to 8.1)	15.7 (7.7 to 31.7)	7.3 (6.3 to 15.1)

End point values	ES: Cohort 5	ES Paired Biopsy: Cohort 6	Chordoma: Cohort 7	ES 1600 mg: Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	69	18	7
Units: Weeks				
median (confidence interval 95%)	23.7 (14.7 to 25.7)	16.1 (8.4 to 16.6)	24.0 (6.3 to 175.3)	39.9 (4.1 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Progression-Free Survival (PFS) Rate at Weeks 24, 32 and 56

End point title	All Cohorts: Progression-Free Survival (PFS) Rate at Weeks 24, 32 and 56

End point description:

PFS was defined as the interval of time between the date of the first dose of study treatment and the earliest date of PD or death due to any cause, whichever comes first, as per RECIST v 1.1 criteria. PFS rate at 24, 32 and 56 weeks were estimated. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as a reference, smallest sum of diameters recorded since the treatment started. In addition, the sum must have an absolute increase from nadir of 5 mm. Estimates were calculated with Kaplan-Meier analysis and 95% CIs using the complementary log-log transformation. ITT population included all participants who received at least 1 dose of tazemetostat.

End point type	Secondary

End point timeframe:

At Weeks 24, 32 and 56

End point values	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3	RMC: Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	32	14
Units: Percentage of participants				
number (confidence interval 95%)				
Week 24	17.6 (6.5 to 33.1)	15.9 (5.1 to 32.0)	34.4 (18.2 to 51.2)	15.4 (2.5 to 38.8)
Week 32	14.1 (4.5 to 28.9)	10.6 (2.2 to 26.7)	26.7 (12.3 to 43.5)	15.4 (2.5 to 38.8)
Week 56	3.5 (0.3 to 15.2)	0.0 (0.0 to 0.0)	13.8 (3.8 to 29.9)	0.0 (0.0 to 0.0)

End point values	ES: Cohort 5	ES Paired Biopsy: Cohort 6	Chordoma: Cohort 7	ES 1600 mg: Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	69	18	7
Units: Percentage of participants				
number (confidence interval 95%)				
Week 24	42.1 (29.3 to 54.4)	33.8 (22.9 to 45.0)	43.6 (18.2 to 66.7)	53.6 (13.2 to 82.5)
Week 32	29.1 (17.9 to 41.2)	29.3 (19.1 to 40.4)	43.6 (18.2 to 66.7)	53.6 (13.2 to 82.5)
Week 56	21.3 (11.6 to 33.0)	22.6 (13.3 to 33.3)	18.2 (1.5 to 50.3)	26.8 (1.3 to 67.0)

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Overall Survival (OS)

End point title	All Cohorts: Overall Survival (OS)

End point description:

OS was defined as the interval of time between the date of the first dose of study treatment and the date of death due to any cause. ITT population included all participants who received at least 1 dose of tazemetostat. Here, '99999' indicates that upper limit of CI was not estimable due to insufficient number of participants with events at study closure.

End point type	Secondary

End point timeframe:

Tumor assessment performed at screening and every 8 weeks beginning at Cycle 3 Day 1, until disease progression or the start of subsequent anti-cancer therapy, whichever occurred first, up to 5.75 years (cycle duration: 28 days)

End point values	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3	RMC: Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	32	14
Units: Weeks				
median (confidence interval 95%)	22.1 (14.4 to 54.6)	43.4 (31.7 to 58.1)	37.9 (23.3 to 104.0)	24.6 (8.4 to 73.6)

End point values	ES: Cohort 5	ES Paired Biopsy: Cohort 6	Chordoma: Cohort 7	ES 1600 mg: Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	69	18	7
Units: Weeks				
median (confidence interval 95%)	82.4 (47.4 to 117.0)	111.4 (63.0 to 99999)	77.7 (32.9 to 99999)	49.6 (19.3 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Overall Survival (OS) Rate at Weeks 24, 32 and 56

End point title	All Cohorts: Overall Survival (OS) Rate at Weeks 24, 32 and 56

End point description:

OS was defined as the interval of time between the date of the first dose of study treatment and the date of death due to any cause. OS rate at 24, 32 and 56 weeks were estimated. Estimates were calculated with Kaplan-Meier analysis and 95% CIs using the complementary log-log transformation. ITT population included all participants who received at least 1 dose of tazemetostat.

End point type	Secondary

End point timeframe:

At Weeks 24, 32 and 56

End point values	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3	RMC: Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	32	14
Units: Percentage of participants				
number (confidence interval 95%)				
Week 24	45.4 (27.6 to 61.6)	81.4 (63.2 to 91.2)	68.8 (49.7 to 81.8)	50.0 (22.9 to 72.2)
Week 32	38.6 (21.8 to 55.2)	68.9 (49.9 to 81.9)	56.3 (37.6 to 71.3)	42.9 (17.7 to 66.0)
Week 56	30.9 (15.5 to 47.7)	37.6 (21.3 to 53.8)	49.6 (31.4 to 65.4)	35.7 (13.0 to 59.4)

End point values	ES: Cohort 5	ES Paired Biopsy: Cohort 6	Chordoma: Cohort 7	ES 1600 mg: Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	69	18	7
Units: Percentage of participants				
number (confidence interval 95%)				
Week 24	85.5 (73.9 to 92.2)	83.6 (72.3 to 90.6)	88.9 (62.4 to 97.1)	83.3 (27.3 to 97.5)
Week 32	77.2 (64.6 to 85.8)	75.8 (63.6 to 84.4)	77.8 (51.1 to 91.0)	66.7 (19.5 to 90.4)
Week 56	57.3 (43.9 to 68.6)	66.5 (53.7 to 76.6)	55.6 (30.5 to 74.8)	44.4 (6.6 to 78.5)

Statistical analyses

No statistical analyses for this end point

Secondary: All Cohorts: Disease Control Rate (DCR) at Weeks 12, 24, 32 and 48

End point title	All Cohorts: Disease Control Rate (DCR) at Weeks 12, 24, 32 and 48

End point description:

DCR was defined as the percentage of participants who achieved a confirmed response (CR or PR, as per RECIST v 1.1 criteria) or who have SD lasting at least 32 weeks from the start of treatment until disease progression or the start of subsequent anti-cancer therapy. CR was defined as disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 mm in the short axis. PR was defined as at least 30% decrease in sum of diameters of target lesions, taking as a reference, baseline sum of diameters. SD was defined neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease. ITT population included all participants who received at least 1 dose of tazemetostat.

End point type	Secondary

End point timeframe:

At Weeks 12, 24, 32 and 48

End point values	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3	RMC: Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	32	14
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	21.9 (9.3 to 40.0)	15.2 (5.1 to 31.9)	40.6 (23.7 to 59.4)	21.4 (4.7 to 50.8)
Week 24	12.5 (3.5 to 29.0)	9.1 (1.9 to 24.3)	21.9 (9.3 to 40.0)	14.3 (1.8 to 42.8)
Week 32	9.4 (2.0 to 25.0)	3.0 (0.1 to 15.8)	18.8 (7.2 to 36.4)	7.1 (0.2 to 33.9)
Week 48	9.4 (2.0 to 25.0)	3.0 (0.1 to 15.8)	12.5 (3.5 to 29.0)	0.0 (0.0 to 23.2)

End point values	ES: Cohort 5	ES Paired Biopsy: Cohort 6	Chordoma: Cohort 7	ES 1600 mg: Cohort 8
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	69	18	7
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	45.2 (32.5 to 58.3)	36.2 (25.0 to 48.7)	50.0 (26.0 to 74.0)	42.9 (9.9 to 81.6)
Week 24	29.0 (18.2 to 41.9)	30.4 (19.9 to 42.7)	33.3 (13.3 to 59.0)	42.9 (9.9 to 81.6)
Week 32	25.8 (15.5 to 38.5)	29.0 (18.7 to 41.2)	27.8 (9.7 to 53.5)	14.3 (0.4 to 57.9)
Week 48	24.2 (14.2 to 36.7)	23.2 (13.9 to 34.9)	11.1 (1.4 to 34.7)	14.3 (0.4 to 57.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts 2 and 8: Objective Response Rate (ORR)

End point title	Cohorts 2 and 8: Objective Response Rate (ORR)[9]

End point description:

ORR was defined as percentage of participants who achieved a confirmed CR or PR based on investigator assessment from start of treatment until PD or start of subsequent anti-cancer therapy or cancer-related surgery, whichever was earlier, as per RANO criteria for primary brain tumors or RECIST v 1.1 criteria for all other solid tumors. CR was defined as disappearance of all target and non-target lesions. Any pathological lymph nodes must be <10 mm in the short axis. PR was defined as at least 30% decrease in sum of diameters of target lesions, taking as a reference, baseline sum of diameters. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as a reference, smallest sum of diameters recorded since the treatment started. In addition, the sum must have an absolute increase from nadir of 5 mm. ITT population included all participants who received at least 1 dose of tazemetostat.

End point type	Secondary

End point timeframe:

Tumor assessment performed at screening and every 8 weeks beginning at Cycle 3 Day 1, until disease progression or the start of subsequent anti-cancer therapy, whichever occurred first, up to 5.75 years

(cycle duration: 28 days)

Notes:

[9] - 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: Only participants in Cohorts 2 and 8 were analyzed for this endpoint.

End point values	Synovial Sarcoma: Cohort 2	ES 1600 mg: Cohort 8		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	7		
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 10.6)	14.3 (0.4 to 57.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs:Day 1 upto 30 days after last dose of study treatment,approximately 88 weeks(Cohort 1),55 weeks(Cohort 2),148 weeks(Cohorts 3 and 8),48 weeks(Cohort 4),304 weeks(Cohort 5),270 weeks(Cohort 6) and 183 weeks(Cohort 7). Deaths: Day 1 up to 5.75 years.

Adverse event reporting additional description:

Safety population included all participants in the ITT population who had at least 1 post-dose safety observation recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Rhabdoid Tumors: Cohort 1

Reporting group description:

Participants with rhabdoid tumors (MRT, RTK, ATRT, and selected tumors with rhabdoid features, including SCCOHT, also known as MRTO) received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Reporting group title	Synovial Sarcoma: Cohort 2

Reporting group description:

Participants with relapsed or refractory synovial sarcoma with SS18-SSX rearrangement received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Reporting group title	Other INI1-negative: Cohort 3

Reporting group description:

Participants with other INI-1-negative tumors or any solid tumor with EZH2 GOF mutation, including EMPNST, EMC, myoepithelial carcinoma, other INI-1-negative malignant tumors with sponsor approval, any solid tumor with EZH2 GOF mutation including but not limited to Ewing’s sarcoma and melanoma received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Reporting group title	RMC: Cohort 4

Reporting group description:

Participants with RMC received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Reporting group title	ES: Cohort 5

Reporting group description:

Participants with ES received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Reporting group title	ES Paired Biopsy: Cohort 6

Reporting group description:

Participants with ES undergoing optional tumour biopsy received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Reporting group title	Chordoma: Cohort 7

Reporting group description:

Participants with poorly differentiated chordoma (or other chordoma with sponsor approval) received tazemetostat 800 mg BID orally in continuous 28-day cycles until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Reporting group title	ES 1600 mg: Cohort 8

Reporting group description:

Participants with ES received tazemetostat 1600 mg QD orally in continuous 28-day cycles until disease

progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study.

Serious adverse events	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 32 (56.25%)	13 / 33 (39.39%)	11 / 32 (34.38%)
number of deaths (all causes)	9	2	5
number of deaths resulting from adverse events	9	2	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 32 (6.25%)	2 / 33 (6.06%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Small cell carcinoma			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	5 / 32 (15.63%)	0 / 33 (0.00%)	4 / 32 (12.50%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 4
Fatigue			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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			
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)	3 / 33 (9.09%)	3 / 32 (9.38%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 32 (6.25%)	0 / 33 (0.00%)	2 / 32 (6.25%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 32 (0.00%)	3 / 33 (9.09%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (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
Acute respiratory failure			
subjects affected / exposed	1 / 32 (3.13%)	2 / 33 (6.06%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Atelectasis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Haemothorax			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (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
Hypercapnia			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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 aspiration			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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 haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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 hypertension			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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			
Confusional state			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Mental status changes			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
C-reactive protein increased			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Ejection fraction decreased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Platelet count decreased			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Ankle fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Femur fracture			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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 fracture			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Tracheal obstruction			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Wound dehiscence			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Pericardial effusion			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Aphasia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Brain oedema			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Cognitive disorder			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Dizziness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Neuralgia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Paraparesis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Seizure			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Febrile neutropenia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 32 (9.38%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 32 (3.13%)	2 / 33 (6.06%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Dysphagia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Large intestinal obstruction			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Hyperbilirubinaemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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			
Blister			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (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
Urinary retention			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Muscular weakness			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (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
Cellulitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyelonephritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 33 (3.03%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Biliary tract infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (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
Periorbital cellulitis			

subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Skin infection			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Soft tissue infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 32 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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
Hypercalcaemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 32 (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
Failure to thrive			

subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (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

Serious adverse events	RMC: Cohort 4	ES: Cohort 5	ES Paired Biopsy: Cohort 6
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 14 (57.14%)	25 / 62 (40.32%)	19 / 69 (27.54%)
number of deaths (all causes)	3	8	6
number of deaths resulting from adverse events	3	8	6
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 14 (0.00%)	3 / 62 (4.84%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 14 (7.14%)	0 / 62 (0.00%)	0 / 69 (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
Small cell carcinoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 14 (21.43%)	4 / 62 (6.45%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 4	0 / 2
Fatigue			

subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Oedema peripheral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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			
Dyspnoea			
subjects affected / exposed	3 / 14 (21.43%)	3 / 62 (4.84%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Pleural effusion			
subjects affected / exposed	0 / 14 (0.00%)	4 / 62 (6.45%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 14 (0.00%)	4 / 62 (6.45%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	2 / 14 (14.29%)	1 / 62 (1.61%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Respiratory distress			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypoxia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Haemothorax			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Hypercapnia			

subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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 haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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 hypertension			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Mental status changes			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Panic attack			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
C-reactive protein increased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 62 (0.00%)	0 / 69 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Ankle fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Femur fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Tracheal obstruction			

subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Wound dehiscence			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Cardiac arrest			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericardial effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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			
Nervous system disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphasia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Brain oedema			

subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Cognitive disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Neuralgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Paraparesis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Seizure			

subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Spinal cord compression			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Ascites			
subjects affected / exposed	1 / 14 (7.14%)	0 / 62 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Vomiting			

subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Ureteric obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Urinary retention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 62 (0.00%)	0 / 69 (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
Muscular weakness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 62 (1.61%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 14 (0.00%)	2 / 62 (3.23%)	0 / 69 (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

Pyelonephritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Bacteraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Biliary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Periorbital cellulitis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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 staphylococcal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Skin infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Soft tissue infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	0 / 69 (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
Hypercalcaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			

subjects affected / exposed	0 / 14 (0.00%)	0 / 62 (0.00%)	0 / 69 (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	Chordoma: Cohort 7	ES 1600 mg: Cohort 8	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 18 (38.89%)	2 / 7 (28.57%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell carcinoma			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 18 (11.11%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fatigue			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal obstruction			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (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	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyelonephritis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rhabdoid Tumors: Cohort 1	Synovial Sarcoma: Cohort 2	Other INI1-negative: Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 32 (84.38%)	28 / 33 (84.85%)	29 / 32 (90.63%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	9 / 32 (28.13%)	8 / 33 (24.24%)	7 / 32 (21.88%)
occurrences (all)	10	13	9
Tumour pain			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	3 / 32 (9.38%)
occurrences (all)	3	2	3
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	4 / 32 (12.50%)
occurrences (all)	0	2	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 32 (21.88%)	10 / 33 (30.30%)	11 / 32 (34.38%)
occurrences (all)	7	13	12
Asthenia			
subjects affected / exposed	3 / 32 (9.38%)	4 / 33 (12.12%)	3 / 32 (9.38%)
occurrences (all)	3	8	3
Oedema peripheral			
subjects affected / exposed	3 / 32 (9.38%)	2 / 33 (6.06%)	1 / 32 (3.13%)
occurrences (all)	4	2	1
Pyrexia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	1 / 32 (3.13%)
occurrences (all)	2	1	1
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 32 (9.38%)	10 / 33 (30.30%)	4 / 32 (12.50%)
occurrences (all)	4	12	6
Dyspnoea			
subjects affected / exposed	7 / 32 (21.88%)	8 / 33 (24.24%)	4 / 32 (12.50%)
occurrences (all)	8	9	4
Pleural effusion			
subjects affected / exposed	3 / 32 (9.38%)	3 / 33 (9.09%)	2 / 32 (6.25%)
occurrences (all)	3	3	4
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 32 (6.25%)	2 / 33 (6.06%)	4 / 32 (12.50%)
occurrences (all)	2	2	4
Investigations			
Weight decreased			
subjects affected / exposed	3 / 32 (9.38%)	2 / 33 (6.06%)	2 / 32 (6.25%)
occurrences (all)	3	5	3
Weight increased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	3 / 32 (9.38%)
occurrences (all)	1	0	3
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 32 (12.50%)	5 / 33 (15.15%)	3 / 32 (9.38%)
occurrences (all)	4	5	5
Dysgeusia			
subjects affected / exposed	3 / 32 (9.38%)	2 / 33 (6.06%)	3 / 32 (9.38%)
occurrences (all)	3	2	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 32 (12.50%)	4 / 33 (12.12%)	4 / 32 (12.50%)
occurrences (all)	7	8	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 32 (31.25%)	9 / 33 (27.27%)	9 / 32 (28.13%)
occurrences (all)	15	14	18
Vomiting			

subjects affected / exposed	13 / 32 (40.63%)	1 / 33 (3.03%)	9 / 32 (28.13%)
occurrences (all)	18	2	12
Constipation			
subjects affected / exposed	7 / 32 (21.88%)	4 / 33 (12.12%)	5 / 32 (15.63%)
occurrences (all)	7	4	5
Diarrhoea			
subjects affected / exposed	6 / 32 (18.75%)	3 / 33 (9.09%)	6 / 32 (18.75%)
occurrences (all)	8	3	6
Abdominal pain			
subjects affected / exposed	4 / 32 (12.50%)	0 / 33 (0.00%)	2 / 32 (6.25%)
occurrences (all)	4	0	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	4 / 32 (12.50%)
occurrences (all)	1	0	4
Dry skin			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	2 / 32 (6.25%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 32 (12.50%)	1 / 33 (3.03%)	6 / 32 (18.75%)
occurrences (all)	6	1	6
Back pain			
subjects affected / exposed	1 / 32 (3.13%)	1 / 33 (3.03%)	1 / 32 (3.13%)
occurrences (all)	1	1	1
Pain in extremity			
subjects affected / exposed	1 / 32 (3.13%)	0 / 33 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	1 / 32 (3.13%)
occurrences (all)	0	2	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	2 / 32 (6.25%)
occurrences (all)	0	1	3
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	3 / 32 (9.38%)	4 / 33 (12.12%)	3 / 32 (9.38%)
occurrences (all)	3	4	4
Hypophosphataemia			
subjects affected / exposed	2 / 32 (6.25%)	3 / 33 (9.09%)	2 / 32 (6.25%)
occurrences (all)	2	4	5

Non-serious adverse events	RMC: Cohort 4	ES: Cohort 5	ES Paired Biopsy: Cohort 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	58 / 62 (93.55%)	65 / 69 (94.20%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 14 (14.29%)	19 / 62 (30.65%)	1 / 69 (1.45%)
occurrences (all)	3	29	1
Tumour pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	4 / 69 (5.80%)
occurrences (all)	0	1	7
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 14 (0.00%)	7 / 62 (11.29%)	4 / 69 (5.80%)
occurrences (all)	0	8	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 14 (21.43%)	24 / 62 (38.71%)	21 / 69 (30.43%)
occurrences (all)	3	38	26
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	4 / 62 (6.45%)	9 / 69 (13.04%)
occurrences (all)	0	6	14
Oedema peripheral			
subjects affected / exposed	2 / 14 (14.29%)	6 / 62 (9.68%)	7 / 69 (10.14%)
occurrences (all)	2	6	8
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	4 / 62 (6.45%)	5 / 69 (7.25%)
occurrences (all)	1	8	6
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 14 (21.43%)	13 / 62 (20.97%)	5 / 69 (7.25%)
occurrences (all)	3	13	6
Dyspnoea			
subjects affected / exposed	4 / 14 (28.57%)	6 / 62 (9.68%)	7 / 69 (10.14%)
occurrences (all)	4	7	11
Pleural effusion			
subjects affected / exposed	3 / 14 (21.43%)	4 / 62 (6.45%)	4 / 69 (5.80%)
occurrences (all)	3	5	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 14 (21.43%)	5 / 62 (8.06%)	4 / 69 (5.80%)
occurrences (all)	3	6	4
Investigations			
Weight decreased			
subjects affected / exposed	4 / 14 (28.57%)	10 / 62 (16.13%)	6 / 69 (8.70%)
occurrences (all)	6	22	12
Weight increased			
subjects affected / exposed	0 / 14 (0.00%)	6 / 62 (9.68%)	3 / 69 (4.35%)
occurrences (all)	0	17	4
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 14 (7.14%)	11 / 62 (17.74%)	5 / 69 (7.25%)
occurrences (all)	1	17	6
Dysgeusia			
subjects affected / exposed	0 / 14 (0.00%)	5 / 62 (8.06%)	1 / 69 (1.45%)
occurrences (all)	0	6	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 14 (28.57%)	10 / 62 (16.13%)	8 / 69 (11.59%)
occurrences (all)	5	34	9
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 14 (21.43%)	23 / 62 (37.10%)	32 / 69 (46.38%)
occurrences (all)	3	31	43
Vomiting			

subjects affected / exposed	5 / 14 (35.71%)	16 / 62 (25.81%)	9 / 69 (13.04%)
occurrences (all)	6	23	13
Constipation			
subjects affected / exposed	4 / 14 (28.57%)	13 / 62 (20.97%)	10 / 69 (14.49%)
occurrences (all)	4	17	10
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	10 / 62 (16.13%)	16 / 69 (23.19%)
occurrences (all)	0	15	17
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	4 / 62 (6.45%)	7 / 69 (10.14%)
occurrences (all)	1	7	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 14 (0.00%)	5 / 62 (8.06%)	7 / 69 (10.14%)
occurrences (all)	0	5	9
Dry skin			
subjects affected / exposed	2 / 14 (14.29%)	5 / 62 (8.06%)	5 / 69 (7.25%)
occurrences (all)	2	6	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 14 (7.14%)	7 / 62 (11.29%)	4 / 69 (5.80%)
occurrences (all)	1	7	6
Back pain			
subjects affected / exposed	2 / 14 (14.29%)	4 / 62 (6.45%)	9 / 69 (13.04%)
occurrences (all)	3	4	10
Pain in extremity			
subjects affected / exposed	1 / 14 (7.14%)	7 / 62 (11.29%)	7 / 69 (10.14%)
occurrences (all)	1	7	7
Musculoskeletal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	11 / 69 (15.94%)
occurrences (all)	0	2	11
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	3 / 62 (4.84%)	5 / 69 (7.25%)
occurrences (all)	0	3	12
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	8 / 14 (57.14%)	15 / 62 (24.19%)	9 / 69 (13.04%)
occurrences (all)	9	27	9
Hypophosphataemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 62 (1.61%)	4 / 69 (5.80%)
occurrences (all)	0	1	5

Non-serious adverse events	Chordoma: Cohort 7	ES 1600 mg: Cohort 8	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)	6 / 7 (85.71%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Tumour pain			
subjects affected / exposed	2 / 18 (11.11%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 18 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 18 (22.22%)	3 / 7 (42.86%)	
occurrences (all)	6	6	
Asthenia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	2 / 18 (11.11%)	3 / 7 (42.86%)	
occurrences (all)	3	3	
Dyspnoea			
subjects affected / exposed	0 / 18 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	9	
Pleural effusion			
subjects affected / exposed	0 / 18 (0.00%)	4 / 7 (57.14%)	
occurrences (all)	0	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 18 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	4	
Weight increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 18 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Dysgeusia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 18 (44.44%)	3 / 7 (42.86%)	
occurrences (all)	10	5	
Vomiting			

subjects affected / exposed	5 / 18 (27.78%)	3 / 7 (42.86%)	
occurrences (all)	5	5	
Constipation			
subjects affected / exposed	3 / 18 (16.67%)	3 / 7 (42.86%)	
occurrences (all)	3	3	
Diarrhoea			
subjects affected / exposed	3 / 18 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	4	2	
Abdominal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Dry skin			
subjects affected / exposed	1 / 18 (5.56%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	2 / 18 (11.11%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	3 / 18 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	2 / 7 (28.57%)	
occurrences (all)	1	4	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	3 / 18 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	3	3	
Hypophosphataemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2015	Protocol changes made to reflect regulatory agency requests, to ensure document consistency and further clarify administrative details.
02 October 2015	Protocol changes made to clarify eligibility, to ensure document consistency and further clarify administrative details.
02 March 2016	To satisfy various regulatory requirements as well as to further expand the criteria for entry into the study and to further simplify and clarify study procedures. Removal of baseline visit (associated assessments to be performed on Day 1 of Cycle 1). Addition of INI-1-negative tumor type cohorts that were exclusively RMC (Cohort 4) and ES (Cohort 5). Participants with previously treated brain metastases might have been included providing they were stable, had no evidence of new or enlarging brain metastases, and were on stable or tapering doses of steroids. Any incidence of secondary lymphoma, even if occurring more than 30 days after the last dose of study treatment, was to be reported to the sponsor. Occurrence of secondary lymphoma added as reason for suspension of enrolment. New section and criteria added detailing removal of participants and study termination. Caution added that participants should avoid prolonged exposure to sunlight and ultraviolet rays while receiving study treatment. Various typographical/ administrative changes made.
25 October 2016	Expanded Cohort 5 (ES) due to clinical activity observed. In addition, the participant population was expanded to include participants with any solid tumor with EZH2 GOF mutation and clarifies that participants with SCCOHT, also known as MRTO were eligible. Clarified relapsed or refractory criteria in synovial sarcoma. Added preliminary pharmacokinetic (PK) data related to cytochrome (CYP)3A metabolism. Added 13-week juvenile Sprague-Dawley rat study data. Clarified disease progression with respect to continuation of treatment. Changed coagulation parameters to remove fibrinogen measurements and add international normalized ratio. Clarified tumor biopsy requirements and definition of disease-related events and adverse events of special interest (AESI). Typographical errors were corrected.
07 August 2017	Added Cohorts 6 (participants with ES undergoing mandatory tumor biopsy) and 7 (participants with chordoma). In addition, the objectives had been reorganized and updated based on recent data and Food and Drug Administration (FDA) meeting. The number of participants expanded to 130 – 250 and typographical errors corrected.
28 September 2018	The protocol was primarily amended with 2 new AESI of T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia (TLL/T-ALL) and myelodysplastic syndrome, as well as the risk mitigation and monitoring required to minimize the risk of occurrence of these events in participants taking tazemetostat.
12 September 2019	To add a new cohort (n=16) of participants with ES that would receive tazemetostat 1600 mg QD, as opposed to all other cohorts receiving 800 mg BID. Rationale for doing so was potential achievement of higher area under the concentration-time curve at steady-state of approximately 7000 nanogram*hour per milliliter due to potentially lower inductive effect of the CYP3A4 enzyme.
21 October 2019	To correct 1600 mg QD tazemetostat dose modification column of Table 2: Dose Modifications for Treatment-Related Toxicities. In amendment 7.0, the restart dose for 1600 mg QD tazemetostat was incorrectly mentioned as BID which was now corrected as QD in amendment 8.0.

17 March 2020	To address requirements of the approval of tazemetostat by the FDA. As part of the post-marketing requirement Epizyme agreed to add 25 additional participants to cohort 6 with a primary endpoint of ORR and 12 months DOR. The number of participants had been updated approximately. The requirement for mandatory tumor biopsies for Cohort 6 was made optional.
01 July 2021	To update the safety profile based on the latest investigator's brochure (IB) (version 11.0) for tazemetostat. Information regarding special situations (overdose, medication error, misuse, and abuse) was clarified and added based on current safety practices. Language regarding the case of TLL/T-ALL was updated to align with the latest IB. Information regarding a case of B-ALL was added to align with the most recent safety profile. The medical monitor was updated. Annual PK assessments were removed with this protocol amendment as the extra PK sample would not yield a sufficient amount of data to characterize the safety and efficacy of tazemetostat, therefore, the collection is no longer needed. Updates were added to the protocol to clarify which study arms were closed for enrolment and that participants in this study (EZH-202) were eligible to rollover into Study EZH-501. Text regarding FDA-approval for tazemetostat was updated to reflect the approval granted after January 2020.
05 October 2022	To update and align background and clinical information about tazemetostat with the updated IB for tazemetostat (IB version 12.0). To update the medical monitor. To update the exploratory objectives and endpoints regarding pharmacodynamics. To remove the requirement for central electrocardiogram readings. To remove the requirements for PK sampling for participants in Cohort 8. To update the requirements for record retention.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported