



Clinical trial results:

An Open-Label, Multicenter, Phase 1/2 Study of Tazemetostat (EZH2 Histone Methyl Transferase [HMT] Inhibitor) as a Single Agent in Subjects With Advanced Solid Tumors or With B-Cell Lymphomas and Tazemetostat in Combination with Prednisolone in Subjects with Diffuse Large B Cell Lymphoma

Summary

EudraCT number	2012-004083-21
Trial protocol	GB DE
Global end of trial date	02 November 2021

Results information

Result version number	v1
This version publication date	18 November 2022
First version publication date	18 November 2022

Trial information

Trial identification

Sponsor protocol code	E7438-G000-101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01897571
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Epizyme, Inc.
Sponsor organisation address	400 Technology Square, Cambridge, Massachusetts, United States, 02139
Public contact	Medical Lead or Designee, Epizyme, Inc., +1 855500-1011, clinicaltrials@epizyme.com
Scientific contact	Medical Lead or Designee, Epizyme, Inc., +1 855500-1011, clinicaltrials@epizyme.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1: To determine the recommended Phase 2 dose (RP2D) of tazemetostat as a single agent administered orally twice daily (BID), continuously in 28-day cycles, in patients with advanced solid tumors or relapsed and/or refractory (R/R) B-cell lymphomas.

Phase 2: To determine the objective response rate [ORR; complete response (CR) + partial response (PR)] of tazemetostat in patients with enhancer of zeste homolog 2 (EZH2) gene mutation positive (MT) or negative [wild-type (WT)] with histologically confirmed diffuse large B-cell lymphoma (DLBCL) or follicular lymphomas (FL) with R/R disease and the ORR of tazemetostat in combination with prednisolone in patients with EZH2 WT DLBCL.

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 abide by Good Clinical Practice as described in the International Conference on Harmonisation Tripartite Guideline E6 (R1), and for United States Investigators, 21 Code of Federal Regulations Parts 50, 54, 56, and 312. 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.

Background therapy:

Phase 2: The DLBCL patients with EZH2 WT received prednisolone 40 milligram per square meter (mg/m²) on Days 1 to 5 and 15 to 19 from Cycle 1 to 4 as background therapy.

Evidence for comparator: -

Actual start date of recruitment	13 June 2013
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: 20
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	France: 255
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Ukraine: 3
Country: Number of subjects enrolled	United Kingdom: 58
Country: Number of subjects enrolled	United States: 34

Worldwide total number of subjects	400
EEA total number of subjects	274

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	196
From 65 to 84 years	198
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This Phase 1/2, open-label study was conducted in patients with advanced solid tumors or with B-cell lymphomas or DLBCL at 39 clinical sites. A total of 401 patients were enrolled in the study. Of which, 400 patients were treated.

Pre-assignment

Screening details:

Phase 1 and Phase 2 part of the study consists a screening period (up to 28 days) followed by continuous 28-day treatment cycles until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Patients who remained on tazemetostat for 24 months or longer and who were eligible were transferred to a rollover study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1

Arm description:

Patients in the Phase 1 portion of the study.

Tazemetostat: Patients who received 100 mg to 1600 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438, E7438
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tazemetostat 100 mg to 1600 mg BID administered orally with or without food in continuous 28-day treatment cycles.

Arm title	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2
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Arm description:

Patients with R/R FL with mutant EZH2 treated with tazemetostat as a single agent in Phase 2 of the study.

Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438, E7438
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tazemetostat 800 mg BID administered orally as 4*200 mg tablets with or without food in continuous 28-day treatment cycles.

Arm title	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
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Arm description:

Patients with R/R FL with WT EZH2 treated with tazemetostat as a single agent in Phase 2 of the study.

Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438, E7438
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tazemetostat 800 mg BID administered orally as 4*200 mg tablets with or without food in continuous 28-day treatment cycles.

Arm title	Phase 2 Group 3: Tazemetostat in R/R DLBCL
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Arm description:

Patients with R/R DLBCL treated with tazemetostat as a single agent or tazemetostat in combination with prednisolone in Phase 2 of the study.

Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Prednisolone: Patients who received 40 mg/m² prednisolone once daily on Days 1 to 5 and 15 to 19 from Cycle 1 to Cycle 4.

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	EPZ-6438, E7438
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Tazemetostat 800 mg BID administered orally as 4*200 mg tablets with or without food in continuous 28-day treatment cycles.

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

Dosage and administration details:

Prednisolone 40 mg/m² once daily was administered on Days 1 to 5 and 15 to 19 from Cycle 1 to Cycle 4.

Number of subjects in period 1	Phase 1	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
Started	64	48	54
Completed	57	0	0
Not completed	7	48	54
Enrolled in rollover study	-	9	8
Consent withdrawn by subject	1	2	2
Adverse event, non-fatal	2	4	5
Reason unknown	-	2	-
Lost to follow-up	-	-	-
Disease Progression	4	31	39

Number of subjects in period 1	Phase 2 Group 3: Tazemetostat in R/R DLBCL
Started	234
Completed	0
Not completed	234
Enrolled in rollover study	10
Consent withdrawn by subject	7
Adverse event, non-fatal	21
Reason unknown	4
Lost to follow-up	1
Disease Progression	191

Baseline characteristics

Reporting groups

Reporting group title	Phase 1
Reporting group description: Patients in the Phase 1 portion of the study. Tazemetostat: Patients who received 100 mg to 1600 mg of tazemetostat, BID, administered in continuous 28-day cycles.	
Reporting group title	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2
Reporting group description: Patients with R/R FL with mutant EZH2 treated with tazemetostat as a single agent in Phase 2 of the study. Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.	
Reporting group title	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
Reporting group description: Patients with R/R FL with WT EZH2 treated with tazemetostat as a single agent in Phase 2 of the study. Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.	
Reporting group title	Phase 2 Group 3: Tazemetostat in R/R DLBCL
Reporting group description: Patients with R/R DLBCL treated with tazemetostat as a single agent or tazemetostat in combination with prednisolone in Phase 2 of the study. Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles. Prednisolone: Patients who received 40 mg/m ² prednisolone once daily on Days 1 to 5 and 15 to 19 from Cycle 1 to Cycle 4.	

Reporting group values	Phase 1	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
Number of subjects	64	48	54
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	54.2 ± 16.11	62.0 ± 8.83	61.1 ± 11.38
Gender categorical Units: Subjects			
Female	26	26	20
Male	38	22	34
Ethnicity			
Unknown or Not Reported category included patients for whom race and/or ethnicity were not obtained due to local privacy regulations.			
Units: Subjects			
Hispanic or Latino	0	0	3
Not Hispanic or Latino	39	38	26
Unknown or Not Reported	25	10	25
Race			
Unknown or Not Reported included patients for whom race and/or ethnicity were not obtained due to local privacy regulations.			

Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	39	33	15
More than one race	0	0	0
Unknown or Not Reported	25	15	38

Reporting group values	Phase 2 Group 3: Tazemetostat in R/R DLBCL	Total	
Number of subjects	234	400	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	63.9		
standard deviation	± 13.63	-	
Gender categorical			
Units: Subjects			
Female	104	176	
Male	130	224	
Ethnicity			
Unknown or Not Reported category included patients for whom race and/or ethnicity were not obtained due to local privacy regulations.			
Units: Subjects			
Hispanic or Latino	4	7	
Not Hispanic or Latino	165	268	
Unknown or Not Reported	65	125	
Race			
Unknown or Not Reported included patients for whom race and/or ethnicity were not obtained due to local privacy regulations.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	4	5	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	99	186	
More than one race	0	0	
Unknown or Not Reported	130	208	

End points

End points reporting groups

Reporting group title	Phase 1
Reporting group description: Patients in the Phase 1 portion of the study. Tazemetostat: Patients who received 100 mg to 1600 mg of tazemetostat, BID, administered in continuous 28-day cycles.	
Reporting group title	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2
Reporting group description: Patients with R/R FL with mutant EZH2 treated with tazemetostat as a single agent in Phase 2 of the study. Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.	
Reporting group title	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
Reporting group description: Patients with R/R FL with WT EZH2 treated with tazemetostat as a single agent in Phase 2 of the study. Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.	
Reporting group title	Phase 2 Group 3: Tazemetostat in R/R DLBCL
Reporting group description: Patients with R/R DLBCL treated with tazemetostat as a single agent or tazemetostat in combination with prednisolone in Phase 2 of the study. Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles. Prednisolone: Patients who received 40 mg/m ² prednisolone once daily on Days 1 to 5 and 15 to 19 from Cycle 1 to Cycle 4.	

Primary: RP2D of Tazemetostat as a Single-Agent and in Combination With Prednisolone (Phase 1 Only)

End point title	RP2D of Tazemetostat as a Single-Agent and in Combination With Prednisolone (Phase 1 Only) ^{[1][2]}
End point description: The RP2D of tazemetostat as administered orally BID, continuously in 28-day cycles in patients with advanced solid tumors or with R/R B-cell lymphomas as determined by incidence, seriousness, toxicity grade, and relatedness of treatment emergent dose limiting toxicities.	
End point type	Primary
End point timeframe: The first 28-day cycle of therapy	

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: Only descriptive statistical analysis was performed for the primary endpoint.

[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: Only patients treated in Phase 1 part of the study were analyzed in this endpoint.

End point values	Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: mg BID				
number (not applicable)	800			

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (CR + PR) (Phase 2)

End point title	Objective Response Rate (CR + PR) (Phase 2) ^{[3][4]}
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End point description:

Number of patients achieving an objective response (CR or PR)/number of patients treated x 100%.

End point type	Primary
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End point timeframe:

Every 8 weeks or sooner, if clinically indicated, until documentation of disease progression.

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: Only descriptive statistical analysis was performed for the primary endpoint.

[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 patients treated in Phase 2 part of the study were analyzed in this endpoint.

End point values	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2	Phase 2 Group 3: Tazemetostat in R/R DLBCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	54	234	
Units: patients	34	19	38	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) for Tazemetostat as a Single-Agent or in Combination With Prednisolone (Phase 2 Only)

End point title	Duration of Response (DOR) for Tazemetostat as a Single-Agent or in Combination With Prednisolone (Phase 2 Only) ^[5]
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End point description:

The time (in months) from the date of the initial response (CR or PR, whichever was first) until the date of the first documented disease progression per an Independent Review Committee (for Groups 1 and 2), per Investigator (Group 3), or death due to any cause. Patients who were alive and progression free at the time of the analysis were censored at the last date where the patient was known to be in response. Note: The DOR was censored, meaning data collection was stopped early for analysis, making the top limit of the 95% confidence interval not estimable (NE). Note: The DOR for some patients was censored, meaning data collection was stopped early for analysis making the top limit of the 95% confidence interval NE. 99999 = NE.

End point type	Secondary
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End point timeframe:

From first dose to last visit

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients treated in Phase 2 part of the study were analyzed in this endpoint.

End point values	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2	Phase 2 Group 3: Tazemetostat in R/R DLBCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	19	38	
Units: months				
median (confidence interval 95%)	11.3 (7.2 to 99999)	13.0 (5.6 to 99999)	5.7 (3.7 to 11.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) for Tazemetostat as a Single-Agent or in Combination With Prednisolone (Phase 2 Only)

End point title	Progression-Free Survival (PFS) for Tazemetostat as a Single-Agent or in Combination With Prednisolone (Phase 2 Only) ^[6]
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End point description:

The time (in months) from the date of first dose of tazemetostat until the earliest date of disease progression or death from any cause. Note: The PFS was censored, meaning data collection was stopped early for analysis.

End point type	Secondary
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End point timeframe:

From first dose to last visit

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only patients treated in Phase 2 part of the study were analyzed in this endpoint.

End point values	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2	Phase 2 Group 3: Tazemetostat in R/R DLBCL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	54	234	
Units: months				
median (confidence interval 95%)	13.8 (10.9 to 22.1)	11.1 (3.7 to 14.6)	1.9 (1.8 to 2.0)	

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored throughout the study starting at time of first dose of tazemetostat until 30 days after discontinuation of study treatment or until initiation of subsequent anticancer therapy if sooner than 30 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Phase 1
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Reporting group description:

Patients in the Phase 1 portion of the study.

Tazemetostat: Patients who received 100 mg to 1600 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Reporting group title	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2
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Reporting group description:

Patients with R/R FL with mutant EZH2 treated with tazemetostat as a single agent in Phase 2 of the study.

Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Reporting group title	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
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Reporting group description:

Patients with R/R FL with mutant EZH2 treated with tazemetostat as a single agent in Phase 2 of the study.

Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Reporting group title	Phase 2 Group 3: Tazemetostat in R/R DLBCL
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Reporting group description:

Patients with R/R DLBCL treated with tazemetostat as a single agent or tazemetostat in combination with prednisolone in Phase 2 of the study.

Tazemetostat: Patients who received 800 mg of tazemetostat, BID, administered in continuous 28-day cycles.

Prednisolone: Patients who received 40 mg/m² prednisolone once daily on Days 1 to 5 and 15 to 19 from Cycle 1 to Cycle 4.

Serious adverse events	Phase 1	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 64 (29.69%)	14 / 48 (29.17%)	16 / 54 (29.63%)
number of deaths (all causes)	35	3	2
number of deaths resulting from adverse events	7	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			

subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myeloid leukaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Lymphoma transformation			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Malignant melanoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Cancer pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Metastases to lung			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Myelodysplastic syndrome			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Subclavian vein thrombosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Surgical and medical procedures			
Pain management			
subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	0 / 54 (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
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	4 / 64 (6.25%)	0 / 48 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 0

Asthenia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	0 / 54 (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
Pyrexia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Axillary pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Breakthrough pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Chills			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Malaise			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Non-cardiac chest pain			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Prostatitis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Pulmonary embolism			
subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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

Dyspnoea			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Hypoxia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Pleural effusion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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 pulmonary oedema			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Dyspnoea exertional			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Lung disorder			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Mediastinal disorder			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Pneumonitis			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Tonsillar hypertrophy			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Depression			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Confusional state			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Amylase increased			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 creatinine increased			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 uric acid increased			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Creatinine renal clearance abnormal			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 physical condition abnormal			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Liver function test abnormal			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Femoral neck fracture			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Hip fracture			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Toxicity to various agents			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Arrhythmia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 failure			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Diastolic dysfunction			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Pericarditis constrictive			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			

Cervicobrachial syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Neuralgia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Osmotic demyelination syndrome			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Post herpetic neuralgia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Syncope			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Transient global amnesia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
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 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Headache			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Lethargy			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 disorder			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Sciatica			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
VIIth nerve paralysis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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	2 / 64 (3.13%)	0 / 48 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Neutropenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Histiocytosis haematophagic			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Lymphopenia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Ascites			

subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Diarrhoea			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Duodenal obstruction			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Gastric disorder			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Gastric ulcer perforation			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Melaena			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Nausea			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Pancreatitis acute			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Subileus			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Vomiting			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Jaundice cholestatic			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Portal hypertension			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Renal colic			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Renal failure acute			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Renal failure chronic			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anuria			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Haematuria			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 failure			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Musculoskeletal pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Back pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Bone pain			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 in extremity			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 in jaw			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Sepsis			
subjects affected / exposed	2 / 64 (3.13%)	1 / 48 (2.08%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Emphyema			
subjects affected / exposed	1 / 64 (1.56%)	1 / 48 (2.08%)	0 / 54 (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
Lung infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Septic shock			
subjects affected / exposed	1 / 64 (1.56%)	0 / 48 (0.00%)	0 / 54 (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
Herpes zoster			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 48 (2.08%)	0 / 54 (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
Bronchitis			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Bronchopneumonia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Febrile infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Influenza			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Lower respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Oral candidiasis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 syncytial virus infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Rhinovirus infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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 tract infection			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Urosepsis			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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			
Decreased appetite			
subjects affected / exposed	2 / 64 (3.13%)	0 / 48 (0.00%)	0 / 54 (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
Dehydration			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Hyperamylasaemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Hypercalcaemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Hyperglycaemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Hyperuricaemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Hypokalaemia			

subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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
Lactic acidosis			
subjects affected / exposed	0 / 64 (0.00%)	0 / 48 (0.00%)	0 / 54 (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	Phase 2 Group 3: Tazemetostat in R/R DLBCL		
Total subjects affected by serious adverse events			
subjects affected / exposed	131 / 234 (55.98%)		
number of deaths (all causes)	52		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphoma transformation			

subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	4 / 234 (1.71%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Metastases to lung			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral artery occlusion			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subclavian vein thrombosis			

subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Pain management			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	17 / 234 (7.26%)		
occurrences causally related to treatment / all	0 / 21		
deaths causally related to treatment / all	0 / 7		
Asthenia			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 234 (1.71%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Axillary pain			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breakthrough pain			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chills			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	3 / 234 (1.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Hypoxia			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Acute pulmonary oedema			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mediastinal disorder			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pneumonitis			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Amylase increased			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood uric acid increased			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Creatinine renal clearance abnormal			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical condition abnormal			
subjects affected / exposed	3 / 234 (1.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			

subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac failure			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diastolic dysfunction			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis constrictive			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cervicobrachial syndrome			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neuralgia			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osmotic demyelination syndrome			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post herpetic neuralgia			

subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient global amnesia			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			

subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VIIth nerve paralysis			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 234 (2.56%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	15 / 234 (6.41%)		
occurrences causally related to treatment / all	8 / 16		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	3 / 234 (1.28%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	19 / 234 (8.12%)		
occurrences causally related to treatment / all	14 / 20		
deaths causally related to treatment / all	0 / 0		
Histiocytosis haematophagic			

subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphopenia			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 234 (2.56%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal obstruction			

subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastric disorder			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric ulcer perforation			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Large intestinal obstruction			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			

subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jaundice cholestatic			

subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Portal hypertension			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure chronic			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anuria			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Hypercalcaemia of malignancy subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	5 / 234 (2.14%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in jaw			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 234 (1.28%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 234 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Empyema				
subjects affected / exposed	0 / 234 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	3 / 234 (1.28%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 234 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	0 / 234 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 234 (0.85%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	2 / 234 (0.85%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Clostridium difficile colitis				
subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				

subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile infection				
subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	2 / 234 (0.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	2 / 234 (0.85%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophageal candidiasis				
subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oral candidiasis				
subjects affected / exposed	1 / 234 (0.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	3 / 234 (1.28%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperamylasaemia			

subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	1 / 234 (0.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase 1	Phase 2 Group 1: Tazemetostat in R/R FL With Mutant EZH2	Phase 2 Group 2: Tazemetostat in R/R FL With WT EZH2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 64 (85.94%)	43 / 48 (89.58%)	48 / 54 (88.89%)
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	6 / 64 (9.38%)	6 / 48 (12.50%)	2 / 54 (3.70%)
occurrences (all)	8	6	2
Headache			
subjects affected / exposed	3 / 64 (4.69%)	6 / 48 (12.50%)	8 / 54 (14.81%)
occurrences (all)	5	7	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 64 (18.75%)	3 / 48 (6.25%)	10 / 54 (18.52%)
occurrences (all)	18	6	11
Thrombocytopenia			
subjects affected / exposed	10 / 64 (15.63%)	4 / 48 (8.33%)	5 / 54 (9.26%)
occurrences (all)	30	7	9
Neutropenia			
subjects affected / exposed	4 / 64 (6.25%)	4 / 48 (8.33%)	4 / 54 (7.41%)
occurrences (all)	6	4	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	34 / 64 (53.13%)	7 / 48 (14.58%)	12 / 54 (22.22%)
occurrences (all)	47	8	15
Pyrexia			
subjects affected / exposed	4 / 64 (6.25%)	2 / 48 (4.17%)	8 / 54 (14.81%)
occurrences (all)	5	2	10
Oedema peripheral			
subjects affected / exposed	4 / 64 (6.25%)	5 / 48 (10.42%)	3 / 54 (5.56%)
occurrences (all)	4	5	4
Fatigue			
subjects affected / exposed	1 / 64 (1.56%)	9 / 48 (18.75%)	9 / 54 (16.67%)
occurrences (all)	2	11	9

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	13 / 64 (20.31%)	10 / 48 (20.83%)	14 / 54 (25.93%)
occurrences (all)	16	13	15
Vomiting			
subjects affected / exposed	12 / 64 (18.75%)	5 / 48 (10.42%)	7 / 54 (12.96%)
occurrences (all)	13	9	8
Constipation			
subjects affected / exposed	11 / 64 (17.19%)	5 / 48 (10.42%)	3 / 54 (5.56%)
occurrences (all)	12	6	3
Abdominal pain			
subjects affected / exposed	6 / 64 (9.38%)	8 / 48 (16.67%)	5 / 54 (9.26%)
occurrences (all)	8	10	5
Diarrhoea			
subjects affected / exposed	7 / 64 (10.94%)	11 / 48 (22.92%)	10 / 54 (18.52%)
occurrences (all)	8	13	15
Abdominal pain upper			
subjects affected / exposed	2 / 64 (3.13%)	5 / 48 (10.42%)	2 / 54 (3.70%)
occurrences (all)	2	7	2
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 64 (14.06%)	3 / 48 (6.25%)	6 / 54 (11.11%)
occurrences (all)	10	5	7
Cough			
subjects affected / exposed	6 / 64 (9.38%)	7 / 48 (14.58%)	11 / 54 (20.37%)
occurrences (all)	11	10	12
Dyspnoea exertional			
subjects affected / exposed	4 / 64 (6.25%)	1 / 48 (2.08%)	0 / 54 (0.00%)
occurrences (all)	5	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	8 / 64 (12.50%)	3 / 48 (6.25%)	1 / 54 (1.85%)
occurrences (all)	9	3	1
Night sweats			
subjects affected / exposed	5 / 64 (7.81%)	3 / 48 (6.25%)	1 / 54 (1.85%)
occurrences (all)	5	3	1

Alopecia subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 4	11 / 48 (22.92%) 12	7 / 54 (12.96%) 7
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5	4 / 48 (8.33%) 5	3 / 54 (5.56%) 3
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	14 / 64 (21.88%) 15 4 / 64 (6.25%) 4	4 / 48 (8.33%) 7 7 / 48 (14.58%) 9	6 / 54 (11.11%) 9 6 / 54 (11.11%) 8
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 5 4 / 64 (6.25%) 4 2 / 64 (3.13%) 2 0 / 64 (0.00%) 0	5 / 48 (10.42%) 6 6 / 48 (12.50%) 8 4 / 48 (8.33%) 4 13 / 48 (27.08%) 14	2 / 54 (3.70%) 5 9 / 54 (16.67%) 13 5 / 54 (9.26%) 5 7 / 54 (12.96%) 17
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	14 / 64 (21.88%) 16 5 / 64 (7.81%) 5	6 / 48 (12.50%) 6 2 / 48 (4.17%) 2	2 / 54 (3.70%) 2 1 / 54 (1.85%) 1

Non-serious adverse events	Phase 2 Group 3: Tazemetostat in R/R DLBCL		
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Total subjects affected by non-serious adverse events subjects affected / exposed	177 / 234 (75.64%)		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	9 / 234 (3.85%) 9 9 / 234 (3.85%) 10		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	38 / 234 (16.24%) 49 50 / 234 (21.37%) 68 23 / 234 (9.83%) 26		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	31 / 234 (13.25%) 36 32 / 234 (13.68%) 37 20 / 234 (8.55%) 22 30 / 234 (12.82%) 31		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting	45 / 234 (19.23%) 46		

subjects affected / exposed	35 / 234 (14.96%)		
occurrences (all)	40		
Constipation			
subjects affected / exposed	18 / 234 (7.69%)		
occurrences (all)	18		
Abdominal pain			
subjects affected / exposed	24 / 234 (10.26%)		
occurrences (all)	27		
Diarrhoea			
subjects affected / exposed	39 / 234 (16.67%)		
occurrences (all)	49		
Abdominal pain upper			
subjects affected / exposed	10 / 234 (4.27%)		
occurrences (all)	12		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 234 (3.85%)		
occurrences (all)	11		
Cough			
subjects affected / exposed	38 / 234 (16.24%)		
occurrences (all)	44		
Dyspnoea exertional			
subjects affected / exposed	2 / 234 (0.85%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 234 (1.28%)		
occurrences (all)	3		
Night sweats			
subjects affected / exposed	5 / 234 (2.14%)		
occurrences (all)	7		
Alopecia			
subjects affected / exposed	8 / 234 (3.42%)		
occurrences (all)	8		
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	5 / 234 (2.14%) 5		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	9 / 234 (3.85%) 11 20 / 234 (8.55%) 21		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	15 / 234 (6.41%) 18 15 / 234 (6.41%) 18 8 / 234 (3.42%) 8 9 / 234 (3.85%) 13		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	23 / 234 (9.83%) 24 5 / 234 (2.14%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2013	Text was added to clarify that the follow-up schedule for survival was to occur every 12 weeks and to warn of the possibility of phototoxicity during prolonged exposure to sunlight. Additional clarification was added concerning safety data review for the purposes of dose escalation or maximum tolerated dose confirmation, contraception requirements were updated, and an exclusion criterion was added for patients with fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase deficiency.
24 April 2013	An updated description of the container holding the powder used for the oral suspension formulation was added.
19 June 2013	Information about the independent data monitoring committee and tazemetostat tablet formulation used in the study was added. Further, references to "serum" were changed to "plasma" in the text describing biomarker and pharmacogenetic assessments, and clarifying text was added to detail the exposure and pharmacokinetic (PK) parameters for both the tablet and oral suspension formulations. Additional detail was inserted to describe the formulation, strength, and container for the tazemetostat tablets and the required preparation procedures for the powder used in the oral suspension formulation.
22 October 2013	Text was added to clarify that the food effect (FE) and drug-drug interaction (DDI) parts of the study would be performed in parallel; to state that no newly enrolled patients were to receive powder for the oral suspension formulation and that instead, all patients were to receive the tablet formulation; to remove the restriction on the maximum daily tablet dose of 1000 mg; and to update the specified tazemetostat preparation procedures.
24 February 2014	A change was made to allow 6 patients to be enrolled in a cohort if a fourth patient was added and subsequently experienced a DLT. Additionally, text was inserted to specify that no DLTs were reported in the first 2 cohorts, and that therefore, the 2-week waiting period for cohort enrollment was removed from the study requirements. Text was also added to specify bone marrow aspirate/biopsy sample collection procedures for pharmacodynamic assessments and to clarify the process of determining the RP2D. Time points for the collection of blood samples used for PK and pharmacodynamic assessments and skin punch biopsies were added, as was guidance for the required Dose Escalation meeting required after 3 DLT-evaluable patients completed 1 cycle of treatment.
29 August 2014	The study design was changed to include EZH2 WT patients in 4 separate cohorts, with up to 30 patients allowed in each and early in-stream stopping criteria presented based on the response evaluation of 10 patients per cohort. A maximum feasible dose of 1600 mg was introduced, and 2 dose cohorts in the Dose Escalation part of the study were expanded to allow up to 12 patients each. A proposed dose of 200 mg was added for the FE part of the study.
14 October 2014	Bone marrow function requirements were streamlined and made less conservative. Additionally, text describing the timing of the pretreatment Screening period was corrected in the Schedule of Assessments and Procedures.

19 February 2015	<p>Provided the rationale for the RP2D. A cohort of non-germinal-center B-cell-like subtype was included in Phase 2 and revised sample size estimate accordingly. Added details of on specific testing methods for EZH2 mutation and cell of origin for the phase 2 part of the study. Revised inclusion criteria for the phase 2 population to require that patients have R/R disease following at least 2 standard prior treatment regimens and have no curative options with other available therapy or those therapies are contraindicated. Objectives modified to remove clinical benefit rate, which is not a recognized efficacy measure in non-hodgkin lymphoma, and to add DOR, which has more clinical and regulatory relevance. Included an additional exploratory objective measurement of OS to be in line with existing protocol language on survival follow-up. Permitted clinically stable patients who had completed 6 cycles of therapy to have Day 15 assessment by telephone contact and local laboratory assessments. Following feedback from regulatory authorities, patients were no longer required to provide fresh tumor biopsies for the purpose of participation in this study. Modified the dose of tazemetostat to be used for the FE sub study to 400 mg. Requirement for skin punch biopsies was removed. Provided additional clarity that any dose interruption of over 28 days for any reason was to be discussed with the Medical Monitor. Stated the dose of tazemetostat in the DDI sub study as 800 mg. Added collection of anticancer therapies administered after tazemetostat.</p>
21 May 2015	<p>Protocol amended to allow for enrollment of patients ≥ 16 years of age in the FE and DDI sub studies.</p>
15 September 2015	<p>Updated the protocol due to acquisition of the clinical development for tazemetostat by Epizyme from Eisai. Simplified the protocol based on completion of Phase 1 (dose escalation and expansion and FE). Removed fasting restriction based on results of the FE study and included the tazemetostat could be administered with or without food. Added that patients who complete study-required assessments may participate in a rollover study. Updated dose modifications section. No longer required in-clinic visits on Day 15 after Cycle 2, only a telephone contact was required; patients were to have hematology and blood chemistry samples drawn at local laboratory. Changed radiologic tumor assessment to every 12 weeks after Cycle 6 to minimize radiation exposure and more accurately reflect standard of care. Changed screening brain magnetic resonance imaging to "only if clinically indicated". Added that all scans were to be submitted to the imaging core laboratory for quality assessment and archiving for potential independent review. Added the fluorodeoxyglucose-positron emission tomography should be conducted at first indication of CR or PR and that a repeat bone marrow biopsy should be performed at first indication of CR for patients with bone marrow involvement at screening. Modified physical exam to a symptom-directed exam during treatment period. Clarified that AEs and concomitant medications should be collected for 30 days after treatment discontinuation unless a new cancer therapy was started. Clarified the analyses to be conducted for PFS, DOR, and overall survival.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The population PK data from this study were combined with PK data from other studies. The PK samples from the combination of tazemetostat with prednisolone were collected but not analyzed in this study.

Notes: