



Clinical trial results:

A Phase 1b/3 Global, Randomized, Double-blind, Placebo-Controlled Trial of Tazemetostat in Combination With Doxorubicin as Frontline Therapy for Advanced Epithelioid Sarcoma

Summary

EudraCT number	2019-003648-55
Trial protocol	GB CZ BE PL
Global end of trial date	24 June 2025

Results information

Result version number	v1 (current)
This version publication date	01 May 2026
First version publication date	01 May 2026

Trial information

Trial identification

Sponsor protocol code	EZH-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04204941
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Epizyme, Inc.
Sponsor organisation address	One Main St, Cambridge, MA, United States, 02139
Public contact	Medical Director, Ipsen, clinical.trials@ipson.com
Scientific contact	Medical Director, Ipsen, clinical.trials@ipson.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	24 June 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2025
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase 1b: Evaluate the safety and tolerability of tazemetostat in combination with doxorubicin in participants with advanced soft tissue sarcoma and select a dose for further evaluation in Phase 3 (the recommended Phase 3 dose [RP3D]). Phase 3: Evaluate and compare the progression-free survival (PFS) by Independent Review Committee (IRC) in participants with advanced epithelioid sarcoma (ES) treated with tazemetostat + doxorubicin versus placebo + doxorubicin.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Conference on Harmonisation Consolidated Guideline on good clinical practice and in compliance with Institutional Review Board/Independent Ethics Committee and informed consent regulations and the Sponsor's policy on bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 December 2019
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	Canada: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	25
EEA total number of subjects	0

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)	19
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase (Ph) 1b/3, 2-part study was conducted at 8 sites in 3 countries in participants with advanced ES. The study consisted of 2 parts: Phase 1b (dose escalation [esc] and dose expansion [exp]) and Phase 3. A total of 25 participants were enrolled in Phase 1b (dose escalation) of the study.

Pre-assignment

Screening details:

Following consultation with Food and Drug Administration(FDA),study was terminated due to feasibility concerns related to inability to meet required enrollment targets. Decision was made after completion of Ph1b(dose esc) & prior to initiation of Ph1b (dose exp) & Ph3. At termination, no participants enrolled in Ph1b (dose exp) & Ph3 not initiated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg

Arm description:

Participants received doxorubicin 75 milligram per square meter (mg/m²) intravenous (IV) injection on Day 1 of Cycles 1 to 6 and tazemetostat 400 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and twice daily (BID) from Day 2 Cycle 1 until disease progression (PD), unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6.

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

Dosage and administration details:

Participants received tazemetostat 400 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1.

Arm title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg
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Arm description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 600 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Arm type	Experimental
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Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6.

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

Dosage and administration details:

Participants received tazemetostat 600 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1.

Arm title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
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Arm description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 800 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6.

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

Dosage and administration details:

Participants received tazemetostat 800 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1.

Number of subjects in period 1	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
Started	4	6	15
Completed	0	0	1
Not completed	4	6	14
Consent withdrawn by subject	-	-	1
Completion of 2 years post treatment follow-up	-	2	5
Death	4	4	7
Unspecified	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg
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Reporting group description:

Participants received doxorubicin 75 milligram per square meter (mg/m²) intravenous (IV) injection on Day 1 of Cycles 1 to 6 and tazemetostat 400 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and twice daily (BID) from Day 2 Cycle 1 until disease progression (PD), unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg
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Reporting group description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 600 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
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Reporting group description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 800 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Reporting group values	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
Number of subjects	4	6	15
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	73.3 ± 6.99	50.5 ± 13.63	46.9 ± 12.14
Gender categorical Units: Subjects			
Female	2	5	9
Male	2	1	6
Ethnicity Units: Subjects			
Hispanic or Latino	0	4	2
Not Hispanic or Latino	4	2	13
Unknown or Not Reported	0	0	0
Race Units: Subjects			
White	4	5	14
American Indian or Alaska Native	0	1	0
Other	0	0	1

Reporting group values	Total		
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Number of subjects	25		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	16		
Male	9		
Ethnicity			
Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	19		
Unknown or Not Reported	0		
Race			
Units: Subjects			
White	23		
American Indian or Alaska Native	1		
Other	1		

End points

End points reporting groups

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg
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Reporting group description:

Participants received doxorubicin 75 milligram per square meter (mg/m²) intravenous (IV) injection on Day 1 of Cycles 1 to 6 and tazemetostat 400 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and twice daily (BID) from Day 2 Cycle 1 until disease progression (PD), unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg
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Reporting group description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 600 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
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Reporting group description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 800 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Subject analysis set title	Phase 1b: Dose Exp: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Participants planned to receive doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 800 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was planned to be 21 days.

Subject analysis set title	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg
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Subject analysis set type	Per protocol
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Subject analysis set description:

Participants planned to receive doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 800 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was planned to be 21 days.

Subject analysis set title	Phase 3: Doxorubicin 75 mg/m ² + Placebo
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Subject analysis set type	Per protocol
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Subject analysis set description:

Participants planned to receive doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and placebo matched to tazemetostat tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was planned to be 21 days.

Primary: Phase 1b: Dose Escalation and Dose Expansion: Number of Participants With Dose-Limiting Toxicities (DLTs)

End point title	Phase 1b: Dose Escalation and Dose Expansion: Number of Participants With Dose-Limiting Toxicities (DLTs) ^[1]
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End point description:

DLT: study drug related adverse event (AE) graded using Common Terminology Criteria for Adverse Events version 5.0: hematological toxicity: Grade (G) 4 neutropenia ≥ 7 days; G3 neutropenia ≥ 14 days; any G neutropenia with normal absolute neutrophil count with fever (>38.5 degree Celsius); G4 thrombocytopenia ≥ 7 days; G3 thrombocytopenia ≥ 14 days with bleeding requiring intervention; anemia \geq G3 requiring transfusion; non-hematological: any drug-related AE \geq G3, G3 fatigue, or 2-point decline in Eastern Cooperative Oncology Group performance status >7 days, G3 aspartate aminotransferase (AST)/G3 alanine aminotransferase (ALT), elevation of >3 days, or G4 AST or

any duration; \geq G3 neurotoxicity or cardiotoxicity; G2 hypersensitivity reaction; nausea, vomiting, or diarrhea \geq 72 hours with adequate antiemetic & other supportive care; any participant meeting Hy's law criteria; any G3 or higher non-hematological toxicity. DLT population. Due to early study termination, Phase 1b (dose expansion) never initiated.

End point type	Primary
End point timeframe:	
From the first dose of study drug (Day 1) up to Day 21 of Cycle 1 (each cycle was 21 days) (dose escalation)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

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

End point values	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Taze metostat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Taze metostat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Taze metostat 800 mg	Phase 1b: Dose Exp: Doxorubicin 75 mg/m ² +Taze metostat 800 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	4	6	6	0 ^[2]
Units: participants	0	1	1	

Notes:

[2] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Primary: Phase 3: Progression-Free Survival Assessed by Independent Review Committee

End point title	Phase 3: Progression-Free Survival Assessed by Independent Review Committee ^[3]
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End point description:

PFS was planned to be assessed in Phase 3. PFS as assessed by IRC was defined as the time from the date of randomization into the study to the first observation of documented PD or death due to any cause, whichever occurred first. PD was defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the study drug started (percent change from nadir, where nadir was defined as the smallest sum of diameters recorded since study drug started). In addition, the sum must have an absolute increase from nadir of 5 millimeter (mm). Due to early study termination, Phase 3 was never initiated.

End point type	Primary
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End point timeframe:

Assessments were planned to be performed within 7 days prior to Day 1 of odd numbered cycles until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Approximately 287.7 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: PFS was a primary endpoint for the Phase 3 element of the study. As the study was terminated before the Phase 3 element was started, this endpoint was not assessed.

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[4]	0 ^[5]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[4] - Due to early study termination, no participants were analyzed.

[5] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Dose Escalation and Dose Expansion: Area Under the Concentration-Time Curve From Time 0 to 24 Hours (AUC0-24) of Tazemetostat

End point title	Phase 1b: Dose Escalation and Dose Expansion: Area Under the Concentration-Time Curve From Time 0 to 24 Hours (AUC0-24) of Tazemetostat
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End point description:

Blood samples were planned to be collected at specified timepoints to evaluate AUC0-24 of tazemetostat. The study was early terminated prior to the data collection and analysis of the pharmacokinetic (PK) parameters for Phase 1b (dose escalation and dose expansion).

End point type	Secondary
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End point timeframe:

Assessments were planned at 0 hour on Days -1, 1, 8 and 21 of Cycle 1; 0, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours post-dose on Days -1, 1, and 21 of Cycle 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Taze metostat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Taze metostat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Taze metostat 800 mg	Phase 1b: Dose Exp: Doxorubicin 75 mg/m ² +Taze metostat 800 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0 ^[6]	0 ^[7]	0 ^[8]	0 ^[9]
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

[6] - Due to early study termination, no participants were analyzed.

[7] - Due to early study termination, no participants were analyzed.

[8] - Due to early study termination, no participants were analyzed.

[9] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Dose Escalation and Dose Expansion: Area Under the Concentration-Time Curve From Time 0 to Last Measurement (AUC0-last) of Tazemetostat

End point title	Phase 1b: Dose Escalation and Dose Expansion: Area Under the Concentration-Time Curve From Time 0 to Last Measurement (AUC0-last) of Tazemetostat
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End point description:

Blood samples were planned to be collected at specified timepoints to evaluate AUC0-last of tazemetostat. The study was early terminated prior to the data collection and analysis of the PK parameters for Phase 1b (dose escalation and dose expansion).

End point type	Secondary
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End point timeframe:

Assessments were planned at 0 hour on Days -1, 1, 8 and 21 of Cycle 1; 0, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours post-dose on Days -1, 1, and 21 of Cycle 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg	Phase 1b: Dose Exp: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0 ^[10]	0 ^[11]	0 ^[12]	0 ^[13]
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

[10] - Due to early study termination, no participants were analyzed.

[11] - Due to early study termination, no participants were analyzed.

[12] - Due to early study termination, no participants were analyzed.

[13] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b: Dose Escalation and Dose Expansion: Maximum Concentration (Cmax) of Tazemetostat

End point title	Phase 1b: Dose Escalation and Dose Expansion: Maximum Concentration (Cmax) of Tazemetostat
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End point description:

Blood samples were planned to be collected at specified timepoints to evaluate Cmax of tazemetostat. The study was early terminated prior to the data collection and analysis of the PK parameters for Phase 1b (dose escalation and dose expansion).

End point type	Secondary
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End point timeframe:

Assessments were planned at 0 hour on Days -1, 1, 8 and 21 of Cycle 1; 0, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours post-dose on Days -1, 1, and 21 of Cycle 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg	Phase 1b: Dose Exp: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	0 ^[14]	0 ^[15]	0 ^[16]	0 ^[17]
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()	()	()

Notes:

[14] - Due to early study termination, no participants were analyzed.

[15] - Due to early study termination, no participants were analyzed.

[16] - Due to early study termination, no participants were analyzed.

[17] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Overall Survival (OS)

End point title	Phase 3: Overall Survival (OS)
End point description:	
OS was planned to be assessed in Phase 3. OS was defined as the number of months elapsed between the date of randomization and the date of death (whatever the cause). Due to early study termination, Phase 3 was never initiated.	
End point type	Secondary
End point timeframe:	
Assessments were planned from the first dose of study drug (Day 1) up to date of death due to any cause, approximately 287.7 weeks	

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[18]	0 ^[19]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[18] - Due to early study termination, no participants were analyzed.

[19] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Phase 3: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)
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End point description:

TEAEs and TSEAEs were planned to be assessed in Phase 3. An AE was any untoward medical occurrence in a participant or clinical investigation participant administered a medicinal product and which did not necessarily had a causal relationship with this study drug. An SAE was any AE that any dose, resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event. A TEAE was an AE that started or worsened in severity on or after the date of the first dose of tazemetostat (study day -1) through 30 days after the end of study drug (doxorubicin or tazemetostat, whichever was dosed last). Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned from first dose of study drug (tazemetostat) (Day -1) up to approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[20]	0 ^[21]		
Units: participants				

Notes:

[20] - Due to early study termination, no participants were analyzed.

[21] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Progression-Free Survival Assessed by Investigator

End point title	Phase 3: Progression-Free Survival Assessed by Investigator
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End point description:

PFS was planned to be assessed in Phase 3. PFS as assessed by Investigator was defined as the time from the date of randomization into the study to the first observation of documented PD or death due to any cause, whichever occurred first. PD was defined as at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the study drug started (percent change from nadir, where nadir was defined as the smallest sum of diameters recorded since study drug started). In addition, the sum must have an absolute increase from nadir of 5 mm. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned to be performed within 7 days prior to Day 1 of odd numbered cycles until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[22]	0 ^[23]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[22] - Due to early study termination, no participants were analyzed.

[23] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Disease Control Rate (DCR)

End point title	Phase 3: Disease Control Rate (DCR)
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End point description:

DCR was planned to be assessed in Phase 3. DCR was defined as percentage of participants with best overall response (BOR) of complete response (CR), partial response (PR), or stable disease (SD) lasting 24 or more weeks. BOR was defined as CR, PR, SD, PD, or not evaluable (NE) which occurred between date of randomization and date of documented PD or date of subsequent therapy. CR was defined as disappearance of all target lesions, any pathological lymph nodes must be <10 mm in short axis. PR was defined as at least a 30% decrease in sum of diameters of target lesions, taking as a reference, baseline sum of diameters. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned to be performed within 7 days prior to Day 1 of odd numbered cycles until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[24]	0 ^[25]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[24] - Due to early study termination, no participants were analyzed.

[25] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Objective Response Rate (ORR)

End point title	Phase 3: Objective Response Rate (ORR)
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End point description:

ORR was planned to be assessed in Phase 3. ORR was defined as the percentage of participants with BOR of CR or PR. BOR was defined as CR, PR, SD, PD, or NE which occurred between date of randomization and date of documented PD or date of subsequent therapy. CR was defined as disappearance of all target lesions, any pathological lymph nodes must be <10 mm in short axis. PR was defined as at least a 30% decrease in sum of diameters of target lesions, taking as a reference, baseline sum of diameters. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned to be performed within 7 days prior to Day 1 of odd numbered cycles until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[26]	0 ^[27]		
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[26] - Due to early study termination, no participants were analyzed.

[27] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Duration of Response (DOR)

End point title	Phase 3: Duration of Response (DOR)
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End point description:

DOR was planned to be assessed in Phase 3. DOR was defined as the time from first documented evidence of CR or PR (whichever response was observed first) to the time of first documented PD or death, whichever occurred first. CR was defined as disappearance of all target lesions, any pathological lymph nodes must be <10 mm in short axis. PR was defined as at least a 30% decrease in sum of diameters of target lesions, taking as a reference, baseline sum of diameters. PD was defined at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, smallest sum of diameters recorded since study drug started. In addition, sum must have an absolute increase from nadir of 5 mm. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned to be performed within 7 days prior to Day 1 of odd numbered cycles until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[28]	0 ^[29]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[28] - Due to early study termination, no participants were analyzed.

[29] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Change From Baseline in European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30): Physical Function, Role Function, and Global Health Status Domains

End point title	Phase 3: Change From Baseline in European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30): Physical Function, Role Function, and Global Health Status Domains
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End point description:

EORTC-QLQ-C30 was planned to be assessed in Phase 3. EORTC-QLQ-C30 measured cancer participants' physical, psychological, and social functions. It consisted of 30 questions incorporated into 5 functional domains (physical,role,social,emotional,and cognitive functioning),9 symptom scales (pain,fatigue,financial impact,appetite loss,nausea and vomiting,diarrhea,constipation,sleep disturbance,and quality of life [QoL]) and a single global QoL/global health status score.Items in functional and symptom scale used raw participant response of 1-4; 1:"not at all" and 4:"very much". 2 global items contained responses ranging from 1:"very poor" to 7:"excellent".All domain scores were transformed in range from 0 to 100;higher functional score indicated more favorable outcomes and higher score on symptom domains indicated a less favorable participant outcome.Baseline:last non-missing assessment prior to starting tazemetostat. Due to early study termination, Phase 3 was never

End point type	Secondary
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End point timeframe:

Assessments were planned at baseline (Day -1) and up to approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[30]	0 ^[31]		
Units: score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[30] - Due to early study termination, no participants were analyzed.

[31] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Progression-Free Survival 2 (PFS2)

End point title	Phase 3: Progression-Free Survival 2 (PFS2)
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End point description:

PFS2 was planned to be assessed in Phase 3. PFS2 was defined as time from the date of the first dose of the next-line therapy to the first observation of PD or death due to any cause, whichever occurred first. PD was defined at least a 20% increase in the sum of the diameters of target lesions, taking as a reference, smallest sum of diameters recorded since study drug started. In addition, sum must have an absolute increase from nadir of 5 mm. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned to be performed within 7 days prior to Day 1 of odd numbered cycles until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[32]	0 ^[33]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[32] - Due to early study termination, no participants were analyzed.

[33] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Time to First Subsequent Therapy (TFST)

End point title	Phase 3: Time to First Subsequent Therapy (TFST)
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End point description:

TFST was planned to be assessed in Phase 3. TFST was defined as the time from the date of randomization to date of first documented administration of a new anti-cancer therapy. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned to be performed within 7 days prior to Day 1 of odd numbered cycles until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Approximately 287.7 weeks

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[34]	0 ^[35]		
Units: months				

median (confidence interval 95%)	(to)	(to)		
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Notes:

[34] - Due to early study termination, no participants were analyzed.

[35] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Oral Clearance (CL/F) of Tazemetostat

End point title	Phase 3: Oral Clearance (CL/F) of Tazemetostat
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End point description:

Blood samples were planned to be collected at specified timepoints to evaluate CL/F of tazemetostat. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned at 0 hour, 0.5 to 2 and 3 to 6 hours post-dose on Days 1 and 8 of Cycles 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[36]	0 ^[37]		
Units: liter/h				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[36] - Due to early study termination, no participants were analyzed.

[37] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Oral Volume of Distribution (Vss) of Tazemetostat

End point title	Phase 3: Oral Volume of Distribution (Vss) of Tazemetostat
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End point description:

Blood samples were planned to be collected at specified timepoints to evaluate Vss of tazemetostat. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned at 0 hour, 0.5 to 2 and 3 to 6 hours post-dose on Days 1 and 8 of Cycles 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[38]	0 ^[39]		
Units: liter				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[38] - Due to early study termination, no participants were analyzed.

[39] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Area Under the Concentration-Time Curve at Steady State (AUC_{ss}) of Tazemetostat

End point title	Phase 3: Area Under the Concentration-Time Curve at Steady State (AUC _{ss}) of Tazemetostat
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End point description:

Blood samples were planned to be collected at specified timepoints to evaluate AUC_{ss} of tazemetostat. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned at 0 hour, 0.5 to 2 and 3 to 6 hours post-dose on Days 1 and 8 of Cycles 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[40]	0 ^[41]		
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[40] - Due to early study termination, no participants were analyzed.

[41] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Trough Concentration (C_{trough}) of Tazemetostat

End point title	Phase 3: Trough Concentration (C _{trough}) of Tazemetostat
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End point description:

Blood samples were planned to be collected at specified timepoints to evaluate C_{trough} of tazemetostat. Due to early study termination, Phase 3 was never initiated.

End point type	Secondary
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End point timeframe:

Assessments were planned at 0 hour, 0.5 to 2 and 3 to 6 hours post-dose on Days 1 and 8 of Cycles 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[42]	0 ^[43]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[42] - Due to early study termination, no participants were analyzed.

[43] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 3: Maximum Concentration of Tazemetostat

End point title	Phase 3: Maximum Concentration of Tazemetostat
End point description: Blood samples were planned to be collected at specified timepoints to evaluate Cmax of tazemetostat. Due to early study termination, Phase 3 was never initiated.	
End point type	Secondary

End point timeframe:

Assessments were planned at 0 hour, 0.5 to 2 and 3 to 6 hours post-dose on Days 1 and 8 of Cycles 1 and on Day 1 of Cycle 2; 0 hour on Day 1 of Cycles 3 and 5

End point values	Phase 3: Doxorubicin 75 mg/m ² + Tazemetostat 800 mg	Phase 3: Doxorubicin 75 mg/m ² + Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[44]	0 ^[45]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[44] - Due to early study termination, no participants were analyzed.

[45] - Due to early study termination, no participants were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs: First dose of study drug (tazemetostat) (Day -1) up to 30 days after last dose of study drug, up to 107 weeks for phase 1b (dose esc). Deaths: First dose of study drug (tazemetostat) (Day -1) up to approximately 287.7 weeks (phase 1b [dose esc]).

Adverse event reporting additional description:

The safety population included all participants who received any dose of study drug. Due to early study termination, Phase 1b (dose expansion) and Phase 3 were never initiated.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	28.0
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Reporting groups

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg
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Reporting group description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 400 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg
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Reporting group description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 600 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Reporting group title	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
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Reporting group description:

Participants received doxorubicin 75 mg/m² IV injection on Day 1 of Cycles 1 to 6 and tazemetostat 800 mg tablet orally single dose on Days -1 and 1 of Cycle 1, Day 1 of Cycle 2 and BID from Day 2 Cycle 1 until PD, unacceptable toxicity, withdrawal of consent, or termination of the study. Each cycle duration was 21 days.

Serious adverse events	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemetostat 800 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	5 / 6 (83.33%)	8 / 15 (53.33%)
number of deaths (all causes)	4	4	8
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiomyopathy acute			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 15 (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
Headache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 15 (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
Presyncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 6 (50.00%)	3 / 15 (20.00%)
occurrences causally related to treatment / all	1 / 1	4 / 4	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	2 / 15 (13.33%)
occurrences causally related to treatment / all	1 / 1	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
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			
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 15 (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
Psychiatric disorders			
Mental status changes			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 15 (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
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 15 (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
Product issues			
Device dislocation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 15 (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

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

Non-serious adverse events	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemeto stat 400 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemeto stat 600 mg	Phase 1b: Dose Esc: Doxorubicin 75 mg/m ² +Tazemeto stat 800 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	6 / 6 (100.00%)	15 / 15 (100.00%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Fatigue			
subjects affected / exposed	3 / 4 (75.00%)	5 / 6 (83.33%)	9 / 15 (60.00%)
occurrences (all)	4	8	12
Oedema peripheral			
subjects affected / exposed	2 / 4 (50.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	3	0	2
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 6 (50.00%)	3 / 15 (20.00%)
occurrences (all)	0	4	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Dyspnoea			

subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 6 (0.00%) 0	2 / 15 (13.33%) 2
Hiccups subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 6 (16.67%) 1	1 / 15 (6.67%) 1
Hypoxia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 6 (16.67%) 1	0 / 15 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 6 (16.67%) 1	0 / 15 (0.00%) 0
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 6 (0.00%) 0	0 / 15 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	3 / 15 (20.00%) 3
Confusional state subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 6 (0.00%) 0	0 / 15 (0.00%) 0
Delirium subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 6 (0.00%) 0	0 / 15 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 6 (16.67%) 1	3 / 15 (20.00%) 3
Investigations Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	6 / 15 (40.00%) 12
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 6 (16.67%) 2	2 / 15 (13.33%) 4
Weight decreased			

subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	2 / 15 (13.33%)
occurrences (all)	2	2	2
White blood cell count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	5 / 15 (33.33%)
occurrences (all)	1	0	13
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Wound secretion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	4 / 15 (26.67%)
occurrences (all)	0	1	4
Headache			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	9 / 15 (60.00%)
occurrences (all)	1	4	11
Taste disorder			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 4 (100.00%)	4 / 6 (66.67%)	10 / 15 (66.67%)
occurrences (all)	6	29	20
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Neutropenia			
subjects affected / exposed	4 / 4 (100.00%)	6 / 6 (100.00%)	8 / 15 (53.33%)
occurrences (all)	11	15	18
Thrombocytopenia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	2 / 15 (13.33%)
occurrences (all)	0	10	6
Eye disorders			

Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	2 / 15 (13.33%)
occurrences (all)	1	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Constipation			
subjects affected / exposed	3 / 4 (75.00%)	5 / 6 (83.33%)	6 / 15 (40.00%)
occurrences (all)	3	5	7
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	5 / 15 (33.33%)
occurrences (all)	1	3	7
Dyspepsia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 6 (33.33%)	6 / 15 (40.00%)
occurrences (all)	2	2	7
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	2 / 15 (13.33%)
occurrences (all)	0	2	2
Haemorrhoids			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Mouth ulceration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	3
Nausea			

subjects affected / exposed occurrences (all)	4 / 4 (100.00%) 5	4 / 6 (66.67%) 5	14 / 15 (93.33%) 29
Oral pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 6 (33.33%) 2	3 / 15 (20.00%) 3
Stomatitis subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 7	4 / 6 (66.67%) 10	9 / 15 (60.00%) 17
Vomiting subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 4	4 / 6 (66.67%) 7	7 / 15 (46.67%) 13
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 6 (33.33%) 2	4 / 15 (26.67%) 4
Dermatitis acneiform subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 6 (0.00%) 0	3 / 15 (20.00%) 3
Night sweats subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 6 (33.33%) 2	0 / 15 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	2 / 6 (33.33%) 2	3 / 15 (20.00%) 4
Renal and urinary disorders			
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 6 (16.67%) 1	0 / 15 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	1 / 6 (16.67%) 2	3 / 15 (20.00%) 5
Back pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2	0 / 6 (0.00%) 0	1 / 15 (6.67%) 3
Joint swelling			

subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 6 (16.67%)	1 / 15 (6.67%)
occurrences (all)	2	2	1
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	4 / 15 (26.67%)
occurrences (all)	0	2	5
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	3 / 15 (20.00%)
occurrences (all)	1	1	5
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	3 / 6 (50.00%)	2 / 15 (13.33%)
occurrences (all)	0	6	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 4 (75.00%)	3 / 6 (50.00%)	2 / 15 (13.33%)
occurrences (all)	3	3	2
Dehydration			
subjects affected / exposed	2 / 4 (50.00%)	3 / 6 (50.00%)	1 / 15 (6.67%)
occurrences (all)	3	3	1
Hypertriglyceridaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	2 / 4 (50.00%)	4 / 6 (66.67%)	4 / 15 (26.67%)
occurrences (all)	2	12	6
Hypomagnesaemia			

subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	1 / 15 (6.67%)
occurrences (all)	3	6	2
Hyponatraemia			
subjects affected / exposed	2 / 4 (50.00%)	2 / 6 (33.33%)	0 / 15 (0.00%)
occurrences (all)	2	2	0
Hypophosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	1 / 15 (6.67%)
occurrences (all)	2	5	2
Malnutrition			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	0 / 15 (0.00%)
occurrences (all)	1	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2019	Added PK sampling windows and adjusted timing of samples which were to be collected on Day 1 of Cycles 3 and 5 (instead of Cycles 4 and 6) to coincide with 6-week tumor measurements. Moved baseline clinical laboratory tests from Day 1 to Day -1 (to occur before the first dose of tazemetostat) and corrected inconsistencies in clinical laboratory test days and test facility (local or central). Changed EORTC-QLQ-C30 questionnaire to Day 1 of all Cycles (instead of just Cycles 1, 2, 4, and 6) in the Phase 3 portion of the study, removed it from Day 8 of Cycles 1 and 2, and specified the domains that would be analyzed. Specified that unblinding would take place at the end of the study except in case of emergency or related adverse event of special interest (AESI) (as intended), rather than at PD. Modified first and second tazemetostat dose reduction levels for combination treatment related toxicities to be consistent with the 200 mg tablet strength. Specified doxorubicin dosing over 3 to 10 minutes or up to approximately 30 minutes to reflect both label instructions and standard of care. Required that any archival tumor tissue samples be obtained less than 1 year before enrolment. Revised categories for AE causality assessments. Corrected inconsistencies between different sections of the protocol, added clarity and enhanced readability.
24 January 2020	Updated inclusion criteria to include immunophenotypic panel (for example: cluster of differentiation (CD34), epithelial membrane antigen, Keratin, and integrase interactor 1) for epithelioid sarcoma as a diagnostic criterion. Updated exclusion criteria to remove human immunodeficiency virus and human T-cell lymphotropic virus 1. Updated Response Evaluation Criteria in Solid Tumors criteria version. Updated prohibited medications to restrict dexrazoxane administration during Cycle 1. Provided clarity regarding doxorubicin administration for Cycles 1-6. Updated Phase 3 sample size determination. Updated decision rules for interim analysis.
03 July 2020	Responded to agency request dated 02 July 2020 regarding eligibility age in Phase 1b dose escalation, Phase 1b dose expansion, and Phase 3 portions of the study. Clarified and updated dose modifications for tazemetostat, "study drug" (blinded Phase 3), and study drug + doxorubicin, modifications for doxorubicin-related toxicity and modifications for combination treatment related toxicities. Updated contraception requirement. Updated restrictions during study treatment.
10 March 2021	Incorporated the RP3D. Included the rationale for RP3D. Updated inclusion and exclusion criteria. Updated dose modifications, interruptions, and discontinuations. Updated study schema and schedule of events for Phase 1b and Phase 3 study. Updated statistical analysis section.
29 March 2022	Corrected statements concerning the Sponsor's response in the event of a new, adult case of related AESI of myelodysplastic syndrome/acute myeloid leukemia or events like myeloproliferative neoplasm. Added that eligible participants enrolled in the open-label Phase 1b portion of the study might be transferred to long-term rollover study EZH-501 at the discretion of the Investigator and Medical Monitor. Modified the electrocardiogram frequency following combination therapy. Modified the duration of monotherapy treatment following combination therapy in the event of surgical resection. Clarified when complete peripheral blood smears were conducted during treatment. Updated language concerning AESIs and safety monitoring by the Sponsor. Made clarifications concerning toxicity management and prophylactic use of hematopoietic colony stimulating factors during the study.

21 March 2023	Supplemented the Phase 1b expansion cohort with approximately 7 additional participants diagnosed with advanced ES, and who would be treated with granulocyte-colony stimulating factor (GCSF) prophylactically in Cycles 1-6. Required prophylactic treatment with GCSF in Cycles 1-6 for all Phase 3 participants. Updated contraception language and information regarding AEs under investigation or of special interest with tazemetostat to align with the current tazemetostat Investigator's Brochure, version 12.0. Included a window of +/-7 days for the 12-week follow-up visits. Updated the list of responsible personnel and emergency contact information. Updated the supplier of doxorubicin to allow sourcing from commercial supply. Added a subsection to define prior and concomitant medications and adjusted the timing of collection to those administered within 30 days before the first study drug dose. Added specifications for data protection and remote source data verification. Added the Sponsor to the list of those at whose discretion participants might be transferred to long-term rollover study EZH-501.
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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.

Following consultation with FDA, study was terminated due to feasibility concerns related to inability to meet required enrollment targets. Decision made after completion of Ph1b (dose esc) & prior to initiation of Ph1b (dose exp) & Ph3.

Notes: