



## 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 |
|-----------------------|---------|

##### 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                                                                       |
| <b>Arm title</b>             | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 400 mg |

Arm description:

Participants received doxorubicin 75 milligram per square meter (mg/m<sup>2</sup>) 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/m<sup>2</sup> 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.

|                  |                                                                           |
|------------------|---------------------------------------------------------------------------|
| <b>Arm title</b> | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 600 mg |
|------------------|---------------------------------------------------------------------------|

Arm description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 |
|----------|--------------|

|                                        |                        |
|----------------------------------------|------------------------|
| 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/m<sup>2</sup> 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.

|                  |                                                                           |
|------------------|---------------------------------------------------------------------------|
| <b>Arm title</b> | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 800 mg |
|------------------|---------------------------------------------------------------------------|

Arm description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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/m<sup>2</sup> 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.

| <b>Number of subjects in period 1</b>          | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 400 mg | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 600 mg | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +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 <sup>2</sup> +Tazemetostat 400 mg |
|-----------------------|---------------------------------------------------------------------------|

Reporting group description:

Participants received doxorubicin 75 milligram per square meter (mg/m<sup>2</sup>) 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 <sup>2</sup> +Tazemetostat 600 mg |
|-----------------------|---------------------------------------------------------------------------|

Reporting group description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> +Tazemetostat 800 mg |
|-----------------------|---------------------------------------------------------------------------|

Reporting group description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> +Tazemetostat 400 mg | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 600 mg | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 800 mg |
|------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Number of subjects                 | 4                                                                         | 6                                                                         | 15                                                                        |
| Age categorical<br>Units: Subjects |                                                                           |                                                                           |                                                                           |

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

|                        |       |  |  |
|------------------------|-------|--|--|
| Reporting group values | Total |  |  |
|------------------------|-------|--|--|

|                                  |    |  |  |
|----------------------------------|----|--|--|
| 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 <sup>2</sup> +Tazemetostat 400 mg |
|-----------------------|---------------------------------------------------------------------------|

#### Reporting group description:

Participants received doxorubicin 75 milligram per square meter (mg/m<sup>2</sup>) 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 <sup>2</sup> +Tazemetostat 600 mg |
|-----------------------|---------------------------------------------------------------------------|

#### Reporting group description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> +Tazemetostat 800 mg |
|-----------------------|---------------------------------------------------------------------------|

#### Reporting group description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> +Tazemetostat 800 mg |
|----------------------------|---------------------------------------------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

#### Subject analysis set description:

Participants planned to receive doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> + Tazemetostat 800 mg |
|----------------------------|-----------------------------------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

#### Subject analysis set description:

Participants planned to receive doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> + Placebo |
|----------------------------|-----------------------------------------------------|

|                           |              |
|---------------------------|--------------|
| Subject analysis set type | Per protocol |
|---------------------------|--------------|

#### Subject analysis set description:

Participants planned to receive doxorubicin 75 mg/m<sup>2</sup> 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) <sup>[1]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------|

#### 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  $\geq 7$  days; G3 neutropenia  $\geq 14$  days; any G neutropenia with normal absolute neutrophil count with fever ( $>38.5$  degree Celsius); G4 thrombocytopenia  $\geq 7$  days; G3 thrombocytopenia  $\geq 14$  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:<br>Doxorubicin 75 mg/m <sup>2</sup> +Taze metostat 400 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75 mg/m <sup>2</sup> +Taze metostat 600 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75 mg/m <sup>2</sup> +Taze metostat 800 mg | Phase 1b: Dose Exp:<br>Doxorubicin 75 mg/m <sup>2</sup> +Taze metostat 800 mg |
|-----------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Subject group type          | Reporting group                                                               | Reporting group                                                               | Reporting group                                                               | Subject analysis set                                                          |
| Number of subjects analysed | 4                                                                             | 6                                                                             | 6                                                                             | 0 <sup>[2]</sup>                                                              |
| 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 <sup>[3]</sup> |
|-----------------|--------------------------------------------------------------------------------------------|

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 |
|----------------|---------|

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.

|                                  |                                                                             |                                                              |  |  |
|----------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| <b>End point values</b>          | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
| Subject group type               | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed      | 0 <sup>[4]</sup>                                                            | 0 <sup>[5]</sup>                                             |  |  |
| 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 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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

|                                                     |                                                                                           |                                                                                           |                                                                                           |                                                                                           |
|-----------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| <b>End point values</b>                             | Phase 1b: Dose<br>Esc:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +Taze<br>metostat 400<br>mg | Phase 1b: Dose<br>Esc:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +Taze<br>metostat 600<br>mg | Phase 1b: Dose<br>Esc:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +Taze<br>metostat 800<br>mg | Phase 1b: Dose<br>Exp:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +Taze<br>metostat 800<br>mg |
| Subject group type                                  | Reporting group                                                                           | Reporting group                                                                           | Reporting group                                                                           | Subject analysis set                                                                      |
| Number of subjects analysed                         | 0 <sup>[6]</sup>                                                                          | 0 <sup>[7]</sup>                                                                          | 0 <sup>[8]</sup>                                                                          | 0 <sup>[9]</sup>                                                                          |
| 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 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 400 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 600 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 800 mg | Phase 1b: Dose Exp:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 800 mg |
|-----------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Subject group type                                  | Reporting group                                                              | Reporting group                                                              | Reporting group                                                              | Subject analysis set                                                         |
| Number of subjects analysed                         | 0 <sup>[10]</sup>                                                            | 0 <sup>[11]</sup>                                                            | 0 <sup>[12]</sup>                                                            | 0 <sup>[13]</sup>                                                            |
| 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 |
|-----------------|--------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

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

|                                                     |                                                                              |                                                                              |                                                                              |                                                                              |
|-----------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| <b>End point values</b>                             | Phase 1b: Dose Esc:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 400 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 600 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 800 mg | Phase 1b: Dose Exp:<br>Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 800 mg |
| Subject group type                                  | Reporting group                                                              | Reporting group                                                              | Reporting group                                                              | Subject analysis set                                                         |
| Number of subjects analysed                         | 0 <sup>[14]</sup>                                                            | 0 <sup>[15]</sup>                                                            | 0 <sup>[16]</sup>                                                            | 0 <sup>[17]</sup>                                                            |
| 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                                                                                                  |                                |

|                                  |                                                                    |                                                        |  |  |
|----------------------------------|--------------------------------------------------------------------|--------------------------------------------------------|--|--|
| <b>End point values</b>          | Phase 3:<br>Doxorubicin 75 mg/m <sup>2</sup> + Tazemetostat 800 mg | Phase 3:<br>Doxorubicin 75 mg/m <sup>2</sup> + Placebo |  |  |
| Subject group type               | Subject analysis set                                               | Subject analysis set                                   |  |  |
| Number of subjects analysed      | 0 <sup>[18]</sup>                                                  | 0 <sup>[19]</sup>                                      |  |  |
| 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.

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|                |           |
|----------------|-----------|
| 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

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

**Notes:**

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

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

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**Statistical analyses**

No statistical analyses for this end point

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

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|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| 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.

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|                |           |
|----------------|-----------|
| 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

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| End point values                 | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|----------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type               | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed      | 0 <sup>[22]</sup>                                                           | 0 <sup>[23]</sup>                                            |  |  |
| 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) |
|-----------------|-------------------------------------|

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 |
|----------------|-----------|

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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed       | 0 <sup>[24]</sup>                                                           | 0 <sup>[25]</sup>                                            |  |  |
| 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.

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|                |           |
|----------------|-----------|
| 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

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| End point values                  | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed       | 0 <sup>[26]</sup>                                                           | 0 <sup>[27]</sup>                                            |  |  |
| 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.

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Phase 3: Duration of Response (DOR)**

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|                 |                                     |
|-----------------|-------------------------------------|
| 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.

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|                |           |
|----------------|-----------|
| 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

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| End point values                 | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|----------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type               | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed      | 0 <sup>[28]</sup>                                                           | 0 <sup>[29]</sup>                                            |  |  |
| 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 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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 |
|----------------|-----------|

End point timeframe:

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

| End point values                     | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|--------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                   | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed          | 0 <sup>[30]</sup>                                                           | 0 <sup>[31]</sup>                                            |  |  |
| 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) |
|-----------------|---------------------------------------------|

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 |
|----------------|-----------|

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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|----------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type               | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed      | 0 <sup>[32]</sup>                                                           | 0 <sup>[33]</sup>                                            |  |  |
| 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) |
|-----------------|--------------------------------------------------|

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 |
|----------------|-----------|

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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type          | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed | 0 <sup>[34]</sup>                                                           | 0 <sup>[35]</sup>                                            |  |  |
| Units: months               |                                                                             |                                                              |  |  |

|                                  |        |        |  |  |
|----------------------------------|--------|--------|--|--|
| median (confidence interval 95%) | ( to ) | ( to ) |  |  |
|----------------------------------|--------|--------|--|--|

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 |
|-----------------|------------------------------------------------|

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 |
|----------------|-----------|

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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                                  | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed                         | 0 <sup>[36]</sup>                                                           | 0 <sup>[37]</sup>                                            |  |  |
| 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 |
|-----------------|------------------------------------------------------------|

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 |
|----------------|-----------|

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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                                  | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed                         | 0 <sup>[38]</sup>                                                           | 0 <sup>[39]</sup>                                            |  |  |
| 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 (AUCss) of Tazemetostat

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Phase 3: Area Under the Concentration-Time Curve at Steady State (AUCss) of Tazemetostat |
|-----------------|------------------------------------------------------------------------------------------|

End point description:

Blood samples were planned to be collected at specified timepoints to evaluate AUCss 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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                                  | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed                         | 0 <sup>[40]</sup>                                                           | 0 <sup>[41]</sup>                                            |  |  |
| 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<sub>trough</sub>) of Tazemetostat

|                 |                                                                      |
|-----------------|----------------------------------------------------------------------|
| End point title | Phase 3: Trough Concentration (C <sub>trough</sub> ) of Tazemetostat |
|-----------------|----------------------------------------------------------------------|

End point description:

Blood samples were planned to be collected at specified timepoints to evaluate C<sub>trough</sub> 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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                                  | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed                         | 0 <sup>[42]</sup>                                                           | 0 <sup>[43]</sup>                                            |  |  |
| 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 C <sub>max</sub> 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:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Tazemetostat<br>800 mg | Phase 3:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +<br>Placebo |  |  |
|-----------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------|--|--|
| Subject group type                                  | Subject analysis set                                                        | Subject analysis set                                         |  |  |
| Number of subjects analysed                         | 0 <sup>[44]</sup>                                                           | 0 <sup>[45]</sup>                                            |  |  |
| 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 |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 28.0 |
|--------------------|------|

### Reporting groups

|                       |                                                                           |
|-----------------------|---------------------------------------------------------------------------|
| Reporting group title | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 400 mg |
|-----------------------|---------------------------------------------------------------------------|

Reporting group description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> +Tazemetostat 600 mg |
|-----------------------|---------------------------------------------------------------------------|

Reporting group description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> +Tazemetostat 800 mg |
|-----------------------|---------------------------------------------------------------------------|

Reporting group description:

Participants received doxorubicin 75 mg/m<sup>2</sup> 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 <sup>2</sup> +Tazemetostat 400 mg | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +Tazemetostat 600 mg | Phase 1b: Dose Esc: Doxorubicin 75 mg/m <sup>2</sup> +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          |
| <b>Infections and infestations</b>              |                |                |                |
| 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          |
| <b>Product issues</b>                           |                |                |                |
| 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 %

| <b>Non-serious adverse events</b>                           | Phase 1b: Dose Esc:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +Tazemeto<br>stat 400 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +Tazemeto<br>stat 600 mg | Phase 1b: Dose Esc:<br>Doxorubicin 75<br>mg/m <sup>2</sup> +Tazemeto<br>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%)                                                                   |
| <b>Vascular disorders</b>                                   |                                                                                     |                                                                                     |                                                                                     |
| 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                                                                                   |
| <b>General disorders and administration site conditions</b> |                                                                                     |                                                                                     |                                                                                     |
| 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                                                                                   |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |                                                                                     |                                                                                     |                                                                                     |
| 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<br>occurrences (all)                                                 | 1 / 4 (25.00%)<br>1 | 0 / 6 (0.00%)<br>0  | 2 / 15 (13.33%)<br>2  |
| Hiccups<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 4 (25.00%)<br>1 | 1 / 6 (16.67%)<br>1 | 1 / 15 (6.67%)<br>1   |
| Hypoxia<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 4 (25.00%)<br>1 | 1 / 6 (16.67%)<br>1 | 0 / 15 (0.00%)<br>0   |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                           | 1 / 4 (25.00%)<br>1 | 1 / 6 (16.67%)<br>1 | 0 / 15 (0.00%)<br>0   |
| Psychiatric disorders<br>Agitation<br>subjects affected / exposed<br>occurrences (all)           | 2 / 4 (50.00%)<br>2 | 0 / 6 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0   |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 3 / 15 (20.00%)<br>3  |
| Confusional state<br>subjects affected / exposed<br>occurrences (all)                            | 2 / 4 (50.00%)<br>2 | 0 / 6 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0   |
| Delirium<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 4 (50.00%)<br>2 | 0 / 6 (0.00%)<br>0  | 0 / 15 (0.00%)<br>0   |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 4 (25.00%)<br>1 | 1 / 6 (16.67%)<br>1 | 3 / 15 (20.00%)<br>3  |
| Investigations<br>Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 6 / 15 (40.00%)<br>12 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 4 (0.00%)<br>0  | 1 / 6 (16.67%)<br>2 | 2 / 15 (13.33%)<br>4  |
| Weight decreased                                                                                 |                     |                     |                       |

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

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

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

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: