



Clinical trial results:

A Phase 1 Study of Pevonedistat (MLN4924), a NEDD8 Activating Enzyme (NAE) Inhibitor, in Combination With Temozolomide and Irinotecan in Pediatric Patients With Recurrent or Refractory Solid Tumors

Summary

EudraCT number	2019-002934-35
Trial protocol	Outside EU/EEA
Global end of trial date	30 September 2020

Results information

Result version number	v1 (current)
This version publication date	29 December 2021
First version publication date	29 December 2021

Trial information

Trial identification

Sponsor protocol code	ADVL1615
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03323034
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Children's Oncology Group
Sponsor organisation address	800 Royal Oaks Dr Suite 210, Monrovia, United States, 91016
Public contact	Thalia Beeles, Children's Oncology Group, tbeeles@childrensoncologygroup.org
Scientific contact	Thalia Beeles, Children's Oncology Group, tbeeles@childrensoncologygroup.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002117-PIP01-17
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	30 September 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of pevonedistat, to define and describe toxicities and to characterize the pharmacokinetics (PK) of pevonedistat.

Protection of trial subjects:

All the participants or parents or patient's guardian were required to read and sign the informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 30
Worldwide total number of subjects	30
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)	1
Children (2-11 years)	13
Adolescents (12-17 years)	12
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at approximately 20 investigative sites in the United States from 13 November 2017 up to 30 September 2020.

Pre-assignment

Screening details:

Pediatric participants diagnosed with recurrent or refractory solid tumors, including CNS tumors and lymphoma were enrolled in the dose escalation study of pevonedistat in a rolling design to receive doses 15, 20, 25, 35 mg/m².

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?	No
Arm title	Pevonedistat15mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²

Arm description:

Pevonedistat 15 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 15 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Pevonedistat IV injection

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan IV injection

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide oral capsules

Arm title	Pevonedistat20mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Arm description:

Pevonedistat 20 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 20 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Pevonedistat IV injection

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide oral capsules

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan IV injection

Arm title	Pevonedistat25mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Arm description:

Pevonedistat 25 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 25 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Pevonedistat IV injection

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide oral capsules

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Irinotecan IV injection	
Arm title	Pevonedistat35mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²

Arm description:

Pevonedistat 35 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 35 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Pevonedistat IV injection

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan IV injection

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide oral capsules

Number of subjects in period 1	Pevonedistat15mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²	Pevonedistat20mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²	Pevonedistat25mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
Started	6	6	6
Pharmacokinetic (PK) Analysis Set	5	6	6
Completed	0	2	0
Not completed	6	4	6
30 days after last dose of investigational agent	4	3	6
Enrollment onto another COG therapeutic study	2	1	-

Number of subjects in period 1	Pevonedistat35mg/ m ² +Temozolomide 100mg/m ² +Irinotecan50mg/m ²
Started	12
Pharmacokinetic (PK) Analysis Set	12
Completed	0
Not completed	12
30 days after last dose of investigational agent	11
Enrollment onto another COG therapeutic study	1

Baseline characteristics

Reporting groups

Reporting group title	Pevonedistat15mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 15 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 15 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat20mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 20 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 20 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat25mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 25 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 25 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat35mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 35 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 35 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group values	Pevonedistat15mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²	Pevonedistat20mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²	Pevonedistat25mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
Number of subjects	6	6	6
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	13.00 ± 4.56	9.8 ± 6.08	11.3 ± 7.76

Gender categorical			
Units: Subjects			
Male	5	4	2
Female	1	2	4
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	2
White	5	3	4
Unknown or Not Reported	1	1	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	5	6	5
Unknown or Not Reported	1	0	0

Reporting group values	Pevonedistat35mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²	Total	
Number of subjects	12	30	
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	11.3		
standard deviation	± 5.29	-	
Gender categorical			
Units: Subjects			
Male	8	19	
Female	4	11	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	2	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	6	
White	7	19	
Unknown or Not Reported	1	3	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	4	5	
Not Hispanic or Latino	8	24	
Unknown or Not Reported	0	1	

End points

End points reporting groups

Reporting group title	Pevonedistat15mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 15 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 15 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat20mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 20 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 20 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat25mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 25 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 25 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat35mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 35 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 35 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, capsules orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Subject analysis set title	Pevonedistat 15,20,25,35+Temozolomide100+Irinotecan50 mg/m ²
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Pevonedistat 15, 20, 25, 35 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12, along with temozolomide, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 15, 20, 25, 35 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Primary: Maximum Tolerated Dose (MTD) of Pevonedistat in Combination With Irinotecan and Temozolomide

End point title	Maximum Tolerated Dose (MTD) of Pevonedistat in Combination With Irinotecan and Temozolomide ^[1]
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End point description:

The MTD is the maximum dose at which fewer than one-third of participants experience dose limiting

toxicities (DLTs). DLT Analysis Set included all participants who receive all prescribed doses of pevonedistat and at least 85% of the prescribed dose of irinotecan and temozolomide per protocol guidelines and must have the appropriate toxicity monitoring studies performed.

End point type	Primary
End point timeframe:	
Cycle 1 (28-day Cycle)	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Only descriptive statistics was planned to be reported for this endpoint.	

End point values	Pevonedistat 15,20,25,35+Temozolomide100+Irinotecan50 mg/m ²			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: mg/m ²				
number (not applicable)	35			

Statistical analyses

No statistical analyses for this end point

Primary: Recommended Phase 2 Dose (RP2D) of Pevonedistat in Combination with Irinotecan and Temozolomide

End point title	Recommended Phase 2 Dose (RP2D) of Pevonedistat in Combination with Irinotecan and Temozolomide ^[2]
End point description:	
The RP2D is the maximum dose at which fewer than one-third of participants experience dose limiting toxicities (DLTs). DLT Analysis Set included all participants who receive all prescribed doses of pevonedistat and at least 85% of the prescribed dose of irinotecan and temozolomide per protocol guidelines and must have the appropriate toxicity monitoring studies performed.	
End point type	Primary
End point timeframe:	
Cycle 1 (28-day Cycle)	
Notes:	
[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: Only descriptive statistics was planned to be reported for this endpoint.	

End point values	Pevonedistat 15,20,25,35+Temozolomide100+Irinotecan50 mg/m ²			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: mg/m ²				
number (not applicable)	35			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Experienced At Least one Grade 3 or Higher Toxicity by Dose Level

End point title	Percentage of Participants Who Experienced At Least one Grade 3 or Higher Toxicity by Dose Level ^[3]
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End point description:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered drug; it does not necessarily have to have a causal relationship with the treatment. The common terminology criteria for adverse events (CTCAE) version (v) 4.0 includes Grades 1 through 5 where each AE based on this general guideline: Grade 1=Mild, Grade 2=Moderate, Grade 3=Severe, Grade 4=Life-threatening or disabling, Grade 5=Death related to adverse event. Safety Analysis Set included all participants who received at least one dose of the study drug.

End point type	Primary
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End point timeframe:

Up to approximately 4 years

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	12
Units: percentage of participants				
number (not applicable)	83.3	50.0	83.3	50.0

Statistical analyses

No statistical analyses for this end point

Primary: Cmax : Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 1

End point title	Cmax : Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 1 ^[4]
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End point description:

Pharmacokinetic (PK) Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 1 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: ng/mL				
geometric mean (geometric coefficient of variation)	137.2 (± 45.92)	205.6 (± 30.68)	293.0 (± 39.77)	441.9 (± 92.03)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax : Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 8

End point title	Cmax : Maximum Observed Plasma Concentration of Pevonedistat Cycle 1 Day 8 ^[5]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 8 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: ng/mL				
geometric mean (geometric coefficient of variation)	134.5 (± 33.05)	239.0 (± 26.35)	242.1 (± 27.93)	380.6 (± 38.56)

Statistical analyses

No statistical analyses for this end point

Primary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 1

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 1 ^[6]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 1 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: hours (h)				
median (full range (min-max))	1.1 (1 to 2)	1.0 (1 to 1)	1.0 (1 to 1)	1.0 (1 to 2)

Statistical analyses

No statistical analyses for this end point

Primary: Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 8

End point title	Tmax: Time to Reach the Maximum Plasma Concentration (Cmax) of Pevonedistat Cycle 1 Day 8 ^[7]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 8 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: hours (h)				
median (full range (min-max))	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)

Statistical analyses

No statistical analyses for this end point

Primary: AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 1

End point title	AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 1 ^[8]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 1 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	663.2 (± 17.51)	917.3 (± 34.63)	1177.3 (± 18.70)	1869.6 (± 50.98)

Statistical analyses

No statistical analyses for this end point

Primary: AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 8

End point title	AUC (0-24 h): Area Under the Plasma Concentration-Time Curve From Time 0 to Time 24 Hours of Pevonedistat Cycle 1 Day 8 ^[9]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type Primary

End point timeframe:

Pre and Post pevonedistat infusion on Day 8 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	664.3 (± 19.48)	1007.6 (± 35.92)	1042.8 (± 21.08)	1670.2 (± 23.93)

Statistical analyses

No statistical analyses for this end point

Primary: CL/F: Clearance of Pevonedistat Cycle 1 Day 1

End point title CL/F: Clearance of Pevonedistat Cycle 1 Day 1^[10]

End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type Primary

End point timeframe:

Pre and Post pevonedistat infusion on Day 1 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: L/h				
geometric mean (geometric coefficient of variation)	29.8 (± 51.87)	22.8 (± 53.68)	23.1 (± 55.05)	21.5 (± 86.23)

Statistical analyses

No statistical analyses for this end point

Primary: CL/F: Clearance of Pevonedistat Cycle 1 Day 8

End point title	CL/F: Clearance of Pevonedistat Cycle 1 Day 8 ^[11]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 8 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: L/h				
geometric mean (geometric coefficient of variation)	29.8 (± 52.42)	20.7 (± 46.89)	25.8 (± 43.88)	23.9 (± 37.24)

Statistical analyses

No statistical analyses for this end point

Primary: T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 1

End point title	T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 1 ^[12]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 1 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: hours (h)				
median (full range (min-max))	5.0 (3 to 9)	5.4 (4 to 6)	5.3 (5 to 6)	5.2 (4 to 8)

Statistical analyses

No statistical analyses for this end point

Primary: T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 8

End point title	T1/2: Elimination Half-Life of Pevonedistat Cycle 1 Day 8 ^[13]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 8 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: hours (h)				
median (full range (min-max))	5.9 (5 to 8)	5.1 (4 to 7)	5.6 (4 to 8)	4.8 (2 to 9)

Statistical analyses

No statistical analyses for this end point

Primary: AUC(0-infinity) Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 1

End point title	AUC(0-infinity) Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 1 ^[14]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 1 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	706.1 (± 13.27)	952.7 (± 35.46)	1222.3 (± 18.35)	1959.5 (± 49.13)

Statistical analyses

No statistical analyses for this end point

Primary: AUC(0-infinity) Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 8

End point title	AUC(0-infinity) Area Under the Plasma Concentration-Time Curve From Time 0 to Infinity of Pevonedistat Cycle 1 Day 8 ^[15]
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End point description:

PK Analysis Set included all participants in the safety analysis set and for whom at least 1 PK parameter is evaluable.

End point type	Primary
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End point timeframe:

Pre and Post pevonedistat infusion on Day 8 of Cycle 1 (Cycle length = 28 days)

Notes:

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

Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	6	6	12
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	707.3 (± 18.67)	1050.1 (± 38.86)	1091.9 (± 23.63)	1756.9 (± 26.27)

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate as Assessed by Response Evaluation Criteria in Solid Tumors (RECIST)

End point title	Best Overall Response Rate as Assessed by Response Evaluation Criteria in Solid Tumors (RECIST)
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End point description:

Percentage of participants with the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started. Progression is the appearance of one or more new lesions. Response-Evaluable Analysis Set included all participants who received at least 1 dose of study drug, have a Baseline disease assessment, and have at least 1 post-baseline disease assessment.

End point type	Secondary
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End point timeframe:

Up to 4 years

End point values	Pevonedistat15 mg/m ² +Temozolomide100 mg/m ² +Irinotecan50mg/m ²	Pevonedistat20 mg/m ² +Temozolomide100 mg/m ² +Irinotecan50mg/m ²	Pevonedistat25 mg/m ² +Temozolomide100 mg/m ² +Irinotecan50mg/m ²	Pevonedistat35 mg/m ² +Temozolomide100 mg/m ² +Irinotecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	12
Units: percentage of participants				
number (not applicable)	16.7	16.7	0.0	0.0

Statistical analyses

No statistical analyses for this end point

Secondary: Biologic Activity of Pevonedistat in Combination with Irinotecan and Temozolomide

End point title	Biologic Activity of Pevonedistat in Combination with Irinotecan and Temozolomide
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End point description:

AAAA

End point type	Secondary
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End point timeframe:

week 10

End point values	Pevonedistat15 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat20 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat25 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²	Pevonedistat35 mg/m ² +Tem ozolomide100 mg/m ² +Irino tecan50mg/m ²
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[16]	0 ^[17]	0 ^[18]	0 ^[19]
Units: subjects				

Notes:

[16] - The data for this outcome measure is not available as per the planned analysis.

[17] - The data for this outcome measure is not available as per the planned analysis.

[18] - The data for this outcome measure is not available as per the planned analysis.

[19] - The data for this outcome measure is not available as per the planned analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 4 years

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Pevonedistat15mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 15 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, capsules, orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 15 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat20mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 20 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, capsules orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 20 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat25mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 25 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, capsules orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 25 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Reporting group title	Pevonedistat35mg/m ² +Temozolomide100mg/m ² +Irinotecan50mg/m ²
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Reporting group description:

Pevonedistat 35 mg/m², Intravenously (IV) over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and Days 1, 3, 5 on Cycles 2+, along with temozolomide, capsules orally, 100 mg/m² on Days 8-12, and irinotecan 50 mg/m², IV over 90 minutes, administered 1 hour after temozolomide on Days 8-12 in 28 day-Cycle 1. Following Cycle 1, participants received pevonedistat 35 mg/m², IV over 60 minutes on Days 1, 3, and 5 along with temozolomide, orally, 100 mg/m² on Days 1-5, and irinotecan 50 mg/m², IV over 90 minutes, on Days 1-5 in 21 day-Cycle 2 for up to 15 Cycles until disease progression or unacceptable toxicity.

Serious adverse events	Pevonedistat15mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²	Pevonedistat20mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²	Pevonedistat25mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	4 / 6 (66.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Medical procedure			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (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
Pleural effusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
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 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events	Pevonedistat35mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²		
Total subjects affected by serious adverse events			

subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Medical procedure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Pevonedistat15mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²	Pevonedistat20mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²	Pevonedistat25mg/ m ² +Temozolomide 100mg/m ² +Irinotecan 50mg/m ²
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	1 / 6 (16.67%) 1
Hypotension subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2
Hot flush subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Surgical and medical procedures Medical procedure subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	2 / 6 (33.33%) 3	2 / 6 (33.33%) 2
Pyrexia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	2 / 6 (33.33%) 3	6 / 6 (100.00%) 6
Gait disturbance subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	1 / 6 (16.67%) 2
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0
Pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Influenza like illness			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Reproductive tract disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	3	2	4
Nasal congestion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tachypnoea			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 2	0 / 6 (0.00%) 0
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Hallucination			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Personality change			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
White blood cell count decreased			
subjects affected / exposed	5 / 6 (83.33%)	6 / 6 (100.00%)	5 / 6 (83.33%)
occurrences (all)	9	17	19
Alanine aminotransferase increased			
subjects affected / exposed	4 / 6 (66.67%)	5 / 6 (83.33%)	5 / 6 (83.33%)
occurrences (all)	6	13	14
Lymphocyte count decreased			
subjects affected / exposed	6 / 6 (100.00%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	12	4	6
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 6 (16.67%)	6 / 6 (100.00%)	5 / 6 (83.33%)
occurrences (all)	4	14	22
Neutrophil count decreased			
subjects affected / exposed	5 / 6 (83.33%)	4 / 6 (66.67%)	3 / 6 (50.00%)
occurrences (all)	11	12	8
Platelet count decreased			
subjects affected / exposed	3 / 6 (50.00%)	4 / 6 (66.67%)	4 / 6 (66.67%)
occurrences (all)	6	7	10
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Blood creatinine increased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Blood cholesterol increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemoglobin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular access complication			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	1	2	8
Sinus bradycardia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	4	3
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cognitive disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Dyskinesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hemiparesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 6 (100.00%)	5 / 6 (83.33%)	6 / 6 (100.00%)
occurrences (all)	11	14	16
Eosinophilia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2

Eye disorders			
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eyelid function disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 6 (66.67%)	4 / 6 (66.67%)	6 / 6 (100.00%)
occurrences (all)	6	8	9
Nausea			
subjects affected / exposed	5 / 6 (83.33%)	5 / 6 (83.33%)	3 / 6 (50.00%)
occurrences (all)	10	8	6
Vomiting			
subjects affected / exposed	5 / 6 (83.33%)	4 / 6 (66.67%)	4 / 6 (66.67%)
occurrences (all)	12	8	9
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	2	4	4
Constipation			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	2 / 6 (33.33%)
occurrences (all)	3	3	3
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Oral pain			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Anal incontinence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			

subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral pruritus			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Salivary hypersecretion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Small intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Rash maculo-papular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Dysuria			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 6 (16.67%)	3 / 6 (50.00%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Joint range of motion decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Bacteraemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Enterocolitis infectious subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Pneumonia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Rash pustular subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1
Rhinitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0
Metabolism and nutrition disorders			
Hyponatraemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	3 / 6 (50.00%) 4	4 / 6 (66.67%) 4
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	3 / 6 (50.00%) 3	5 / 6 (83.33%) 8
Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 5	0 / 6 (0.00%) 0	4 / 6 (66.67%) 6
Hypocalcaemia			

subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	3	2	3
Decreased appetite			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	3 / 6 (50.00%)
occurrences (all)	4	4	3
Hypokalaemia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	4 / 6 (66.67%)
occurrences (all)	3	2	4
Hypophosphataemia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	4	3	8
Hypermagnesaemia			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	2 / 6 (33.33%)
occurrences (all)	3	2	4
Hypomagnesaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	0	2	4
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	3
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	6
Hyperkalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	4
Hypernatraemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Hypertriglyceridaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Metabolic disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Pevonedistat35mg/ m^2+Temozolomide 100mg/m^2+Irinotecan 50mg/m^2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Medical procedure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	9		
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gait disturbance			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Reproductive tract disorder			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Epistaxis			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hiccups			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tachypnoea			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Personality change			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Investigations			
White blood cell count decreased			
subjects affected / exposed	12 / 12 (100.00%)		
occurrences (all)	21		
Alanine aminotransferase increased			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	14		
Lymphocyte count decreased			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	9		
Aspartate aminotransferase increased			

subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	9		
Neutrophil count decreased			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	13		
Platelet count decreased			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	12		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Blood bicarbonate decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Investigation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood cholesterol increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood urea increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haemoglobin increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Red blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vascular access complication			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			

Sinus tachycardia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Sinus bradycardia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	5		
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cognitive disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dyskinesia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hemiparesis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Paraesthesia			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Tremor subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	9 / 12 (75.00%) 17		
Eosinophilia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Eye disorders Eye pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Eyelid function disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Photophobia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	5 / 12 (41.67%) 9		
Nausea subjects affected / exposed occurrences (all)	6 / 12 (50.00%) 6		
Vomiting subjects affected / exposed occurrences (all)	6 / 12 (50.00%) 10		
Abdominal pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Constipation			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Anal incontinence			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Oral pruritus			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Salivary hypersecretion			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Small intestinal obstruction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Alopecia	subjects affected / exposed	1 / 12 (8.33%)		
	occurrences (all)	2		
Pruritus	subjects affected / exposed	0 / 12 (0.00%)		
	occurrences (all)	0		
Renal and urinary disorders				
Proteinuria	subjects affected / exposed	0 / 12 (0.00%)		
	occurrences (all)	0		
Dysuria	subjects affected / exposed	0 / 12 (0.00%)		
	occurrences (all)	0		
Pollakiuria	subjects affected / exposed	1 / 12 (8.33%)		
	occurrences (all)	1		
Urinary incontinence	subjects affected / exposed	1 / 12 (8.33%)		
	occurrences (all)	1		
Endocrine disorders				
Hypothyroidism	subjects affected / exposed	0 / 12 (0.00%)		
	occurrences (all)	0		
Musculoskeletal and connective tissue disorders				
Back pain	subjects affected / exposed	3 / 12 (25.00%)		
	occurrences (all)	4		
Pain in extremity	subjects affected / exposed	2 / 12 (16.67%)		
	occurrences (all)	2		
Arthralgia	subjects affected / exposed	1 / 12 (8.33%)		
	occurrences (all)	1		
Myalgia	subjects affected / exposed	0 / 12 (0.00%)		
	occurrences (all)	0		

Joint range of motion decreased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Muscle spasms subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Neck pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Bacteraemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Enterocolitis infectious subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Pneumonia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Rash pustular subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Rhinitis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	11		
Hyperglycaemia			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	7		
Hypoalbuminaemia			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	9		
Hypocalcaemia			
subjects affected / exposed	8 / 12 (66.67%)		
occurrences (all)	11		
Decreased appetite			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	5		
Hypokalaemia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Hypophosphataemia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Hypermagnesaemia			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	7		
Hypomagnesaemia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Hyperphosphataemia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Hypoglycaemia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Metabolic disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2018	The following changes were made in amendment 1: - The study committee contact information regulatory address was updated. - Clarifications were made in accordance with update to Common Terminology Criteria for Adverse Events (CTCAE v.5). This included aligning hepatic function and decreased tendon reflexes in eligibility, definitions of dose limiting toxicity, and addition of appendix for protocol specific reference values. - Renal function eligibility criterion was updated. - Language regarding the event of emesis after temozolomide was added as "For infusion related reactions consider premedication with diphenhydramine for subsequent doses and increasing infusion duration to 2 hours. Other supportive care measures may be used at the investigator's discretion." - Pulse oximetry and bone marrow evaluations were added to the table of required observations and to the therapy delivery maps. - The pharmacokinetic (PK) and pharmacodynamic (PD) details were updated. - Drug name, solution preparation/administration instructions and drug interactions were updated; risks were updated in accordance with the RA. - The toxicities for cefixime were administratively updated. - The date of the irinotecan monograph was updated. - The following criterion was added for Off Study: "Patient did not receive protocol treatment after study enrollment." - A typo in age range was corrected. - The definition of evaluable for adverse events was updated for clarity. - Reference to the obsolete Pregnancy form was deleted. - The former Pregnancy Form was removed and replaced with a table of toxicity-specific grading. - List of cytochrome P3A4 (CYP3A4) substrates, inducers, and inhibitors has been administratively updated. - Shipping guidelines were added. - The table was updated to reflect the 99th percentile for consistency with the eligibility criteria.
27 January 2019	The following changes were made in amendment 2: - The adverse events of risk were added to the protocol.
13 March 2019	The following changes were made in amendment 3: - Children's oncology group Phase 1/Pilot Consortium (COGC) was replaced with Children's oncology group Pediatric Early Phase Clinical Trials Network (PEP-CTN). - Pediatric Early Phase Clinical Trials Network (PEP-CTN) logo was added throughout the protocol - Pediatric Early Phase Clinical Trials Network (PEP-CTN) replaced COGC as the lead organization. - Protocol Coordinator contact was updated to Pediatric Early Phase Clinical Trials Network (PEP-CTN) Operations and Data/Statistics - This trial was covered by a Certificate of Confidentiality from the federal government. - PEPCTNAERS@childrensoncologygroup.org - Developmental therapeutics was replaced with Children's oncology group Pediatric Early Phase Clinical Trials Network (COG PEP-CTN) to show that the study was monitored in accordance with PEP-CTN policies for data and safety monitoring. - The upper limit of normal (ULN) for alanine aminotransferase (ALT) is 45 units per litre (U/L) - The ULN for AST is 50 U/L
24 September 2019	The following changes were made in amendment 4: - Toxicity Risk Table has been replaced with National Cancer Institute (NCI) provided Comprehensive Adverse Events and Potential Risks (CAEPR) version 2.2.

10 December 2019	The following changes were made in amendment 5: - Research Coordinator was removed. - Rationale for amendment #5 was added. - Dose Level 4 at 35 mg/m² was added. - Pevonedistat drug formulation was updated - Dilute pevonedistat injection in ... - Once pevonedistat injection is diluted... - Infusion line should be flushed with 5% Dextrose immediately after IV administration is complete. - Patient Care Considerations was added. - Statistical sample size and study duration was updated to include information regarding this amendment. - The Domestic Planned Enrollment Report table was updated to reflect current enrollment on this study. - Dose Level 4 was added to the therapy delivery maps (TDMs).
20 July 2020	The following changes were made in amendment 6: - The preparation, storage, and administration sections were updated per the request for amendment (RA).
27 August 2020	The following changes were made in amendment 7. - Administrative changes made in the committee - Inserted revised CAEPR for MLN4924 (Pevonedistat hydrochloride [HCl]) - Added New Risk: Also Reported on MLN4924 Trials But With Insufficient Evidence for Attribution: Ascites; Hypertension; Non-cardiac chest pain; Treatment related secondary malignancy; Urinary retention; White blood cell decreased. - Increase in Risk Attribution: Changed to Less Likely from Also Reported on MLN4924 Trials But With Insufficient Evidence for Attribution: Urinary tract infection. - Decrease in Risk Attribution: Changed to Less Likely from Likely: Constipation; Dizziness Changed to Also Reported on MLN4924 Trials But With Insufficient Evidence for Attribution from Less Likely: Rash maculo-papular

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported