Clinical trial results:
A Phase 2, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects with Relapsed or Refractory Malignant Mesothelioma with BAP1 loss of function.

Summary

EudraCT number	2016-001139-10
Trial protocol	FR GB
Global end of trial date	25 June 2018

Results information

Result version number	v1 (current)
This version publication date	26 February 2021
First version publication date	26 February 2021

Trial information

Trial identification

Sponsor protocol code	EZH-203

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Part 1 (Pharmacokinetics):
To assess the pharmacokinetic (PK) and safety profile of single (Cycle 1 day 1) and repeated doses (Cycle 1 day 2 onwards) of 800 mg tazemetostat administered as 400 mg tablets in subjects with relapsed or refractory malignant mesothelioma regardless of BRCA1 associated protein 1 (BAP1) status.
Part 2 (Efficacy):
To assess disease control rate (DCR) at 12 weeks (consisting of complete response [CR], partial response [PR], or stable disease [SD]) according to modified Response Evaluation Criteria in Solid Tumors [RECIST] for thoracic disease or RECIST 1.1 elsewhere in subjects with relapsed or refractory BAP1-deficient malignant mesothelioma treated with tazemetostat.

Protection of trial subjects:

The procedures set out in the study protocol pertaining to the conduct, evaluation, and documentation of this study were designed to ensure that the Sponsor and Investigators ae by Good Clinical Practice (GCP) as described in the International Conference on Harmonisation (ICH) Tripartite Guideline E6 (R1). Compliance with these regulations also constituted compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study was also carried out in keeping with local legal and regulatory requirements.
Subject confidentiality was strictly held in trust by the Sponsor and/or their designee(s), participating Investigators, and site staff.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 August 2016
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: 23
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	France: 14
Worldwide total number of subjects	74
EEA total number of subjects	51

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)	31
From 65 to 84 years	42
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening Period extends from Day -21 to Day -1. Screening laboratory assessments may be used as Day 1 assessments if performed within 72 hours of the first dose of study treatment.

Period 1

Period 1 title	Intent-to-Treat (ITT) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Relapsed or refractory MM with or without BAP1-deficiency

Arm description:

Eligible subjects were enrolled into 2 different parts:
• Part 1 – Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status
• Part 2 – Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma

Arm type	Experimental
Investigational medicinal product name	Tazemetostat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects enrolled in Part 1 were to receive a single 800 mg tazemetostat dose on Cycle 1 Day 1. Starting on Cycle 1 Day 2, tazemetostat was to be administered at a dose of 800 mg twice daily (BID). Subjects enrolled in Part 2 were to receive tazemetostat 800 mg BID starting on Cycle 1 Day 1. Subjects continued on study treatment until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study. Subjects may have received tazemetostat for an approximate duration of 12 months.

Number of subjects in period 1	Relapsed or refractory MM with or without BAP1-deficiency
Started	74
Completed	0
Not completed	74
Consent withdrawn by subject	1
Disease progression	65
Death	5
Subject enrolled in rollover study	3

Baseline characteristics

Reporting groups	
Reporting group title	Intent-to-Treat (ITT)

Reporting group description: -

Reporting group values	Intent-to-Treat (ITT)	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	31	31	
From 65-84 years	42	42	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	25	25	
Male	49	49	

Subject analysis sets	
Subject analysis set title	Part 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Part 1: Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status.

Subject analysis set title	Part 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma.

Subject analysis set title	NEEDED for single arm trial statistical comparison
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subject analysis set included only to permit selection as a comparison arm for statistical analysis

Reporting group values	Part 1	Part 2	NEEDED for single arm trial statistical comparison
Number of subjects	13	61	1
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	

Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	24	
From 65-84 years	5	37	
85 years and over	1	0	
Gender categorical Units: Subjects			
Female	3	22	
Male	10	39	

End points

End points reporting groups

Reporting group title	Relapsed or refractory MM with or without BAP1-deficiency
Reporting group description:	
Eligible subjects were enrolled into 2 different parts: • Part 1 – Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status • Part 2 – Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma	
Subject analysis set title	Part 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Part 1: Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status.	
Subject analysis set title	Part 2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects with relapsed or refractory BAP1-deficient malignant mesothelioma.	
Subject analysis set title	NEEDED for single arm trial statistical comparison
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subject analysis set included only to permit selection as a comparison arm for statistical analysis	

Primary: Part 2: Disease control rate [DCR (CR+PR+SD)] at Week 12

End point title	Part 2: Disease control rate [DCR (CR+PR+SD)] at Week 12
End point description:	
The DCR at Week 12 is defined as the percentage of subjects with a response of complete response (CR), partial response (PR) or stable disease (SD) at the Week 12 assessment, as per modified RECIST (Nowak, 2005) for thoracic disease or RECIST 1.1 elsewhere.	
End point type	Primary
End point timeframe:	
At week 12	

End point values	Part 2	NEEDED for single arm trial statistical comparison		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	1		
Units: Subjects	61	1		

Statistical analyses

Statistical analysis title	Disease control rate
Comparison groups	Part 2 v NEEDED for single arm trial statistical comparison

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Disease Control Rate (DCR)
Point estimate	51.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	40
upper limit	62.7

Notes:

[1] - DCR (CR+PR+SD) at Week 12
Subject analysis set "NEEDED for single arm trial statistical comparison" was included only to permit selection as a comparison arm for statistical analysis, as indicated in question 82 of the EudraCT & EU CTR Frequently asked questions.
The given number for 'Number of subjects included in analysis' is automatically calculated and states 62. This is incorrect and the number included in the analysis = 61 subjects.

Primary: Part 1b): Adverse Events and clinical laboratory tests

End point title	Part 1b): Adverse Events and clinical laboratory tests[2]

End point description:

This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point type	Primary

End point timeframe:

Overall trial

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested

End point values	Part 1			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: 1.1				
number (not applicable)	13			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1a): PK parameters

End point title	Part 1a): PK parameters[3]

End point description:

Maximum plasma concentration(Cmax), time of Cmax (Tmax), area under the plasma concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC0-t), AUC from time 0 extrapolated to infinity (AUC0-∞) (single dose only), and the apparent terminal elimination half-life (t1/2) of tazemetostat after administration as 400 mg tablets.

No statistical analysis for this endpoint.

End point type	Primary

End point timeframe:

Day 1, 8 and 15

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: All PK parameters were to be calculated using actual times. Population estimates of CL/F, Vd/F, and Ka for tazemetostat were to be calculated with a non-linear mixed-effects model using NONMEM 7 software. The effect of subject characteristics such as age, weight, body surface area, and gender on the PK parameters may have been investigated. The PK data from this study may be combined with data from other studies to determine the final population PK model.

End point values	Part 1			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: 1.1				
number (not applicable)	13			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on or after the date of first dose of study drug through 30 days after the last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Part 1

Reporting group description:

Subjects with relapsed or refractory malignant mesothelioma regardless of BAP1 status

Reporting group title	Part 2

Reporting group description: -

Serious adverse events	Part 1	Part 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	23 / 61 (37.70%)	
number of deaths (all causes)	1	7	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Air embolism			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericarditis constrictive			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 13 (15.38%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 13 (0.00%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Liver abscess			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1	Part 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	59 / 61 (96.72%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	3 / 13 (23.08%)	18 / 61 (29.51%)	
occurrences (all)	3	33	
Malignant ascites			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	4	
Skin papilloma			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	4	
Deep vein thrombosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Embolism			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 13 (30.77%)	22 / 61 (36.07%)	
occurrences (all)	4	28	
Asthenia			
subjects affected / exposed	1 / 13 (7.69%)	8 / 61 (13.11%)	
occurrences (all)	1	10	
Oedema peripheral			
subjects affected / exposed	1 / 13 (7.69%)	6 / 61 (9.84%)	
occurrences (all)	1	8	

Non-cardiac chest pain			
subjects affected / exposed	0 / 13 (0.00%)	3 / 61 (4.92%)	
occurrences (all)	0	5	
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences (all)	1	3	
Mucosal inflammation			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Catheter site pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Inflammation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Dysmenorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vaginal discharge			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vaginal prolapse			

subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vulvovaginal dryness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 13 (53.85%)	14 / 61 (22.95%)	
occurrences (all)	13	19	
Cough			
subjects affected / exposed	2 / 13 (15.38%)	17 / 61 (27.87%)	
occurrences (all)	2	17	
Dysphonia			
subjects affected / exposed	2 / 13 (15.38%)	3 / 61 (4.92%)	
occurrences (all)	2	3	
Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	3 / 61 (4.92%)	
occurrences (all)	0	3	
Pleural effusion			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences (all)	2	2	
Nasal congestion			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Pulmonary embolism			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Rhinorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Dyspnoea exertional			

subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Rales			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			

subjects affected / exposed	0 / 13 (0.00%)	12 / 61 (19.67%)	
occurrences (all)	0	15	
Blood creatine increased			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	3	
Lymphocyte count decreased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 61 (0.00%)	
occurrences (all)	3	0	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood fibrinogen increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Breath sounds abnormal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
C-reactive protein increased			

subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Neutrophil count increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Joint injury			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Procedural pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Contusion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Muscle strain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Pericardial effusion			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Cardiac tamponade			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Pericarditis constrictive			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Sinus bradycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 13 (0.00%)	8 / 61 (13.11%)	
occurrences (all)	0	11	
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	5	
Headache			
subjects affected / exposed	0 / 13 (0.00%)	3 / 61 (4.92%)	
occurrences (all)	0	4	
Lethargy			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Ataxia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Balance disorder			

subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Cognitive disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Neuralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Tardive dyskinesia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Tremor			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	13 / 61 (21.31%)	
occurrences (all)	0	17	
Leukocytosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Eye disorders			

Dry eye			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Visual acuity reduced			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 13 (46.15%)	15 / 61 (24.59%)	
occurrences (all)	6	22	
Vomiting			
subjects affected / exposed	2 / 13 (15.38%)	15 / 61 (24.59%)	
occurrences (all)	4	18	
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	11 / 61 (18.03%)	
occurrences (all)	2	14	
Abdominal distension			
subjects affected / exposed	2 / 13 (15.38%)	5 / 61 (8.20%)	
occurrences (all)	2	8	
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	7 / 61 (11.48%)	
occurrences (all)	0	7	
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	4 / 61 (6.56%)	
occurrences (all)	1	5	
Dry mouth			
subjects affected / exposed	0 / 13 (0.00%)	3 / 61 (4.92%)	
occurrences (all)	0	3	
Dyspepsia			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences (all)	1	2	
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)	3 / 61 (4.92%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 13 (7.69%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Stomatitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	2	0	
Diverticulum			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Eructation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Large intestine polyp			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 13 (7.69%)	3 / 61 (4.92%)	
occurrences (all)	1	3	
Dermal cyst			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences (all)	1	2	

Night sweats			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	1 / 13 (7.69%)	2 / 61 (3.28%)	
occurrences (all)	1	3	
Dermatitis acneiform			
subjects affected / exposed	1 / 13 (7.69%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Alopecia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Eczema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Intertrigo			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Rash maculo-papular			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	4	
Scar pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	

Skin induration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Skin lesion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Skin mass			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Urine odour abnormal			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 13 (23.08%)	4 / 61 (6.56%)	
occurrences (all)	3	5	
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 61 (1.64%)	
occurrences (all)	2	1	

Muscle spasms			
subjects affected / exposed	0 / 13 (0.00%)	6 / 61 (9.84%)	
occurrences (all)	0	8	
Arthropathy			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
spinal column stenosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	8 / 61 (13.11%)	
occurrences (all)	0	11	
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	5 / 61 (8.20%)	
occurrences (all)	1	5	
Oral candidiasis			
subjects affected / exposed	1 / 13 (7.69%)	3 / 61 (4.92%)	
occurrences (all)	1	3	
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	4 / 61 (6.56%)	
occurrences (all)	0	4	
Nasopharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Oral herpes			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	3	
Rash pustular			

subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)		
occurrences (all)	0	2		
Rhinitis				
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)		
occurrences (all)	0	2		
Vaginal infection				
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)		
occurrences (all)	0	2		
Bronchitis				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Cellulitis				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Cystitis				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Dermatophytosis				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Device related infection				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Gastroenteritis				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Groin abscess				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Infected skin ulcer				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
lung infection				
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)		
occurrences (all)	0	1		
Oropharyngeal candidiasis				

subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Skin infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Viral rhinitis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 13 (15.38%)	22 / 61 (36.07%)	
occurrences (all)	3	27	
Hyperglycaemia			
subjects affected / exposed	1 / 13 (7.69%)	3 / 61 (4.92%)	
occurrences (all)	1	3	
Hyponatraemia			
subjects affected / exposed	0 / 13 (0.00%)	3 / 61 (4.92%)	
occurrences (all)	0	8	
Hypoalbuminaemia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	3	

Hypophosphataemia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Dehydration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	3	
Hypoglycaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2016	• Updated exclusion criteria to exclude Subjects who are pregnant or breastfeeding • Updated dose modification and clarified actions taken in case of a secondary neoplasm • Updated frequency of pregnancy testing • Removed urinalysis for laboratory testing
13 April 2017	•To include feedback obtained from Principal Investigators during site initiation visits • To incorporate changes in study procedures documented as Note to File • To resolve inconsistencies within sections of the protocol • To amend the optional tumor biopsy to an optional paired tumor biopsy • To clarify BAP1 loss inclusion criteria preference for IHC in the mesothelioma tumor sample
27 November 2017	• Updated text on phototoxicity to also include specific measures to avoid UV exposure. • Updated text to clarify subjects' duration of treatment • Updated text on the definition of "post-menopausal" per the definition of The American Association of Clinical Endocrinologists that is most commonly accepted. • Updated text on pregnancy testing to align the text in section 8.3.3.3 with footnote in Table 1: Study assessments

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported