Clinical trial results:
A Phase 1B/2 Study to Evaluate Safety and Clinical Activity of Combinations of Avelumab, Binimetinib and Talazoparib in subjects With Locally Advanced or Metastatic Ras-Mutant Solid Tumors

Summary

EudraCT number	2018-000124-34
Trial protocol	BE
Global end of trial date	02 February 2021

Results information

Result version number	v1 (current)
This version publication date	03 February 2022
First version publication date	03 February 2022

Trial information

Trial identification

Sponsor protocol code	B9991033

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03637491
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc. , +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2020
Global end of trial reached?	Yes
Global end of trial date	02 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the DLT rate of the doublet and triplet combinations in subjects with mPDAC in order to determine the RP2D for the combinations and to assess the ORR of the doublet and triplet combinations based on investigator assessment per RECIST v1.1 in subjects with mPDAC and other KRASor NRAS-mutant advanced solid tumors.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 August 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	31 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Belgium: 3
Worldwide total number of subjects	35
EEA total number of subjects	3

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)	13
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Forty six subjects were screened and 36 were enrolled, of whom 1 was not treated. This study was planned to include 2 periods: Phase 1b and Phase 2. Due to the early termination of this study, only the doublet combinations in Phase 1b to find a safe dose were conducted, and neither the triplet combination of Phase 1b nor Phase 2 was initiated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Avelumab+Binimetinib 30mg (Phase 1b)

Arm description:

Avelumab was administered at a fixed dose of 800 mg every 2 weeks (Q2W) in combination with binimetinib at 30 mg twice daily (BID) orally on a continuous daily dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib was administered at 30 mg twice daily (BID) orally on a continuous daily dosing schedule.

Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	MSB0010718C
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab was administered at a fixed dose of 800 mg every 2 weeks (Q2W).

Arm title	Avelumab+Binimetinib 45mg (Phase 1b)

Arm description:

Avelumab was administered at a fixed dose of 800 mg Q2W in combination with binimetinib at 45 mg BID orally on a continuous daily dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	MSB0010718C
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab was administered at a fixed dose of 800 mg Q2W.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib was administered at 45 mg BID orally on a continuous daily dosing schedule.

Arm title	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)

Arm description:

Binimetinib 30 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Talazoparib
Investigational medicinal product code	
Other name	PF-06944076
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Talazoparib was administered at 0.75 mg once daily (QD) orally on a continuous dosing schedule.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib was administered at 30 mg orally BID (7 days on / 7 days off)

Arm title	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)

Arm description:

Binimetinib 45 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.

Arm type	Experimental
Investigational medicinal product name	Talazoparib
Investigational medicinal product code	
Other name	PF-06944076
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Talazoparib was administered at 0.75 mg once daily (QD) orally on a continuous dosing schedule.

Investigational medicinal product name	Binimetinib
Investigational medicinal product code	
Other name	MEK162
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Binimetinib was administered at 45 mg orally BID (7 days on / 7 days off)

Number of subjects in period 1	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)
Started	10	12	7
Received treatment	10	12	7
Completed	0	0	0
Not completed	10	12	7
Adverse event, serious fatal	9	9	5
Consent withdrawn by subject	1	-	1
Study Terminated By Sponsor	-	2	1
Lost to follow-up	-	1	-

Number of subjects in period 1	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Started	6
Received treatment	6
Completed	0
Not completed	6
Adverse event, serious fatal	3
Consent withdrawn by subject	2
Study Terminated By Sponsor	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab+Binimetinib 30mg (Phase 1b)
Reporting group description:	
Avelumab was administered at a fixed dose of 800 mg every 2 weeks (Q2W) in combination with binimetinib at 30 mg twice daily (BID) orally on a continuous daily dosing schedule.	
Reporting group title	Avelumab+Binimetinib 45mg (Phase 1b)
Reporting group description:	
Avelumab was administered at a fixed dose of 800 mg Q2W in combination with binimetinib at 45 mg BID orally on a continuous daily dosing schedule.	
Reporting group title	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)
Reporting group description:	
Binimetinib 30 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.	
Reporting group title	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Reporting group description:	
Binimetinib 45 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.	

Reporting group values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)
Number of subjects	10	12	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	5	2
From 65-84 years	5	7	5
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	65.30	65.25	68.57
standard deviation	± 11.10	± 8.56	± 9.61
Sex: Female, Male Units: Subjects			
Female	4	3	6
Male	6	9	1
Race/Ethnicity, Customized Units: Subjects			
Asian	1	0	0
White	9	12	6
Not Reported	0	0	1
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	0	0	1
Not Hispanic or Latino	10	12	5
Unknown or Not Reported	0	0	1

Reporting group values	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)	Total	
Number of subjects	6	35	
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)	1	13	
From 65-84 years	5	22	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	68.00		
standard deviation	± 9.94	-	
Sex: Female, Male Units: Subjects			
Female	3	16	
Male	3	19	
Race/Ethnicity, Customized Units: Subjects			
Asian	0	1	
White	5	32	
Not Reported	1	2	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	5	32	
Unknown or Not Reported	1	2	

End points

End points reporting groups

Reporting group title	Avelumab+Binimetinib 30mg (Phase 1b)
Reporting group description:	
Avelumab was administered at a fixed dose of 800 mg every 2 weeks (Q2W) in combination with binimetinib at 30 mg twice daily (BID) orally on a continuous daily dosing schedule.	
Reporting group title	Avelumab+Binimetinib 45mg (Phase 1b)
Reporting group description:	
Avelumab was administered at a fixed dose of 800 mg Q2W in combination with binimetinib at 45 mg BID orally on a continuous daily dosing schedule.	
Reporting group title	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)
Reporting group description:	
Binimetinib 30 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.	
Reporting group title	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Reporting group description:	
Binimetinib 45 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.	

Primary: Number of Subjects with Dose Limiting Toxicities (DLTs) During the Primary DLT Evaluation Period (Cycle 1) in Phase 1b

End point title	Number of Subjects with Dose Limiting Toxicities (DLTs) During the Primary DLT Evaluation Period (Cycle 1) in Phase 1b[1]
End point description:	
Any adverse events (AEs) occurring in the first cycle of treatment (28 days) which were attributable to study drugs and met DLT criteria. DLT was defined as Hematologic: febrile neutropenia; neutropenic infection; Grade >=3 thrombytopenia with bleed; Grade 4 thrombocytopenia; Grade 4 anemia; Non-hematologic: Grade≥3 creatinine phosphokinase (CPK) with creatinine >= 1.5 x baseline; Grade 3 troponin increase with cardiac toxicity; potential Hy's Law cases; Eye disorders: retinal vascular disorder; Grade≥3 uveitis, blurred vision, flashing lights, floaters or others for >21 consecutive days; other Grade 4; Cardiac disorders; Respiratory disorders: bronchospasm Grade 3; Skin and subcutaneous tissue disorders; Non-adherence to treatment schedule; Dose reductions. Analysis population included subjects in Phase 1b who received at least one dose of the combination treatment, and either experienced DLT or completed the DLT observation period for the first cycle of treatment without DLT.	
End point type	Primary
End point timeframe:	
From date of first study treatment to day 28 of study treatment (Up to 28 days)	
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: Statistical analysis was not planned for this endpoint	

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	11	6	5
Units: Subjects	3	5	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events During the On-Treatment Period

End point title	Number of Subjects With Adverse Events During the On-Treatment Period

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. Treatment-emergent adverse event (TEAE) means event between first dose of study treatment and up to 30 days after last dose that were absent before treatment or that worsened relative to pretreatment state. An SAE was an AE resulting in any of death, inpatient hospitalization, life-threatening experience, disability, congenital anomaly or deemed significant for any other reason. Symptoms of infusion-related reactions (IRRs) may include, but were not limited to, fever, chills, flushing, hypotension, dyspnea, wheezing, back pain, abdominal pain, and urticaria. The safety analysis set included all enrolled subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day) assessed for a maximum duration of up to 31 months

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	7	6
Units: Subjects				
TEAEs	10	12	7	6
grade ≥ 3 TEAEs	10	9	4	5
treatment-related TEAEs	10	12	7	6
grade ≥ 3 treatment-related TEAEs	8	4	0	3
serious TEAEs	6	9	3	3
serious treatment-related TEAEs	2	1	0	2
TEAEs leading to discontinuation of Avelumab	1	2	0	0
TEAEs leading to discontinuation of Binimetinib	3	4	1	2
TEAEs leading to discontinuation of Talazoparib	0	0	1	2
TEAEs leading to discontinuation of any drug	3	4	1	2
TEAEs leading to discontinuation of all drugs	1	1	1	0
treatment-related TEAE discontinued by Avelumab	1	1	0	0
treatment-related TEAE discontinued by Binimetinib	3	3	0	1
treatment-related TEAE discontinued by Talazoparib	0	0	0	1
treatment-related TEAE discontinued by any drug	3	3	0	1
treatment-related TEAE discontinued by all drugs	1	0	0	0
TEAEs leading to death	0	3	2	1

treatment-related TEAEs leading to death	0	0	0	0
infusion-related reactions (IRRs)	3	1	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Hematology Laboratory Abnormalities During the On-Treatment Period Graded by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point title	Number of Subjects With Hematology Laboratory Abnormalities During the On-Treatment Period Graded by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point description:

Laboratory abnormalities were graded by NCI CTCAE version 4.03. Anemia, hemoglobin increased, lymphocyte count decreased, lymphocyte count increased, neutrophil count decreased, platelet count decreased and white blood cell decreased were evaluated. This outcome measure calculated the number of subjects with laboratory abnormalities whose maximum on-treatment CTCAE Grade were 1-4. The safety analysis set included all enrolled subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Prior to study drug administration on Days 1 and 15 of each treatment cycle, until 30 days after last dose (assessed for a maximum duration of up to 31 months)

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	7	6
Units: Subjects				
ANEMIA	9	9	7	5
HEMOGLOBIN INCREASED	0	0	1	0
LYMPHOCYTE COUNT DECREASED	6	7	5	6
LYMPHOCYTE COUNT INCREASED	1	1	0	0
NEUTROPHIL COUNT DECREASED	0	1	1	2
PLATELET COUNT DECREASED	3	3	4	3
WHITE BLOOD CELL DECREASED	2	2	0	4

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Chemistry Laboratory Abnormalities During the On-Treatment Period Graded by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point title	Number of Subjects With Chemistry Laboratory Abnormalities During the On-Treatment Period Graded by National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point description:

Laboratory abnormalities were graded by NCI CTCAE version 4.03. Alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, creatine phosphokinase (CPK) increased, creatinine increased, gamma-glutamyl transferase (GGT) increased, hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, lipase increased and serum amylase increased were evaluated. This outcome measure calculated the number of subjects with laboratory abnormalities whose maximum on-treatment CTCAE Grade were 1-4. The safety analysis set included all enrolled subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Prior to study drug administration on Days 1 and 15 of each treatment cycle, until 30 days after last dose (assessed for a maximum duration of up to 31 months)

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	7	6
Units: Subjects				
ALANINE AMINOTRANSFERASE INCREASED	5	5	3	2
ALKALINE PHOSPHATASE INCREASED	9	7	6	5
ASPARTATE AMINOTRANSFERASE INCREASED	8	8	6	3
BLOOD BILIRUBIN INCREASED	4	0	0	1
CPK INCREASED	6	7	3	1
CREATININE INCREASED	8	11	6	4
GGT INCREASED	8	4	6	2
HYPERCALCEMIA	2	1	1	0
HYPERGLYCEMIA	5	6	4	5
HYPERKALEMIA	1	3	1	0
HYPERMAGNESEMIA	0	0	0	0
HYPERNATREMIA	0	0	0	1
HYPOALBUMINEMIA	7	11	5	3
HYPOCALCEMIA	0	1	0	0
HYPOGLYCEMIA	2	2	0	1
HYPOKALEMIA	4	1	3	3
HYPOMAGNESEMIA	3	2	2	1
HYPONATREMIA	5	4	2	0
HYPOPHOSPHATEMIA	3	1	1	0
LIPASE INCREASED	1	3	0	1
SERUM AMYLASE INCREASED	2	5	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Concentration During Multiple Dosing (Ctrough) for Avelumab

End point title	Predose Concentration During Multiple Dosing (Ctrough) for Avelumab[2]

End point description:

Ctrough was the pre-dose concentration during multiple dosing and was directly observed from data. The lower limit of quantification (LLQ) was 0.20 microgram per milliliter. Concentration values below the LLQ were set to zero. Geometric Mean analysis was on the log scale. Zero values were not included in geometric mean and geometric coefficient of variation calculation. The geometric coefficient of variation is expressed in percentage. Number of subjects that started the Arm: subjects who had at least 1 concentration measurement for avelumab. Therefore, only 2 treatment groups including avelumab were analyzed. Number of Subjects Analyzed: subjects who had avelumab concentrations above the LLQ at specific time point.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1, and Day 15 of Cycle 1 (each cycle is 28 days); Day 1 and Day 15 of Cycle 2; and Day 1 of Cycles 3, 5, 9 and 12.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned only for the arms specified.

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: microgram per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
CYCLE1_DAY15	22.38 (± 59)	28.82 (± 57)		
CYCLE2_DAY1	29.26 (± 39)	38.28 (± 52)		
CYCLE2_DAY15	40.86 (± 42)	37.26 (± 59)		
CYCLE3_DAY1	31.30 (± 999999)	34.69 (± 75)		
CYCLE5_DAY1	28.00 (± 999999)	36.51 (± 38)		
CYCLE9_DAY1	999999 (± 999999)	46.49 (± 999999)		
CYCLE12_DAY1	999999 (± 999999)	38.77 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Concentration During Multiple Dosing (Ctrough) for Binimetinib

End point title	Predose Concentration During Multiple Dosing (Ctrough) for Binimetinib

End point description:

Ctrough was directly observed from data. Ctrough = concentration prior to study drug administration. The LLQ was 1.00 ng/mL. Concentration values below the LLQ were set to zero. Geometric Mean analysis was on the log scale. Zero values were not included in geometric mean and geometric coefficient of variation calculation. The geometric coefficient of variation is expressed in percentage.

Number of subjects that started the Arm: subjects who had at least 1 concentration measurement for binimetinib. Number of Subjects Analyzed: subjects who had binimetinib concentration values above the LLQ at specific time point.

End point type	Secondary

End point timeframe:

Predose on Day 15 of Cycle 1 (each cycle is 28 days), Day 1 and Day 15 of Cycle 2, Day 1 of Cycle 3 for avelumab+binimetinib groups, and on Day 8 and Day 15 of Cycle 1, Day 1 of Cycle 2 and Day 1 of Cycle 3 for Binimetinib+Talazoparib groups

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	7	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
CYCLE1_DAY8	999999 (± 999999)	999999 (± 999999)	82.90 (± 999999)	128.6 (± 49)
CYCLE1_DAY15	87.85 (± 48)	88.67 (± 16)	22.80 (± 999999)	999999 (± 999999)
CYCLE2_DAY1	55.71 (± 56)	107.5 (± 999999)	999999 (± 999999)	999999 (± 999999)
CYCLE2_DAY15	93.45 (± 90)	88.33 (± 999999)	999999 (± 999999)	999999 (± 999999)
CYCLE3_DAY1	56.60 (± 999999)	74.90 (± 999999)	999999 (± 999999)	999999 (± 999999)

Statistical analyses

No statistical analyses for this end point

Secondary: Predose Concentration During Multiple Dosing (Ctrough) for Talazoparib

End point title	Predose Concentration During Multiple Dosing (Ctrough) for Talazoparib[3]

End point description:

Ctrough was directly observed from data. Ctrough = concentration prior to study drug administration. The LLQ was 25 pg/mL. Concentration values below the LLQ were set to zero. Geometric Mean analysis was on the log scale. Zero values were not included in geometric mean and geometric coefficient of variation calculation. The geometric coefficient of variation is expressed in percentage. Number of subjects that started the Arm: subjects who had at least 1 concentration measurement for talazoparib. Therefore, only 2 treatment groups including talazoparib were analyzed. Number of Subjects Analyzed: subjects who had talazoparib concentrations above the LLQ at specific time point.

End point type	Secondary

End point timeframe:

Pre-dose on Days 1, 8 and Day 15 of Cycle 1 (each cycle is 28 days), and on Day 1 of Cycle 2 and Cycle 3

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned only for the arms specified.

End point values	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: picograms per millilitre (pg/mL)				
geometric mean (geometric coefficient of variation)				
CYCLE1_DAY8	4856 (± 999999)	2926 (± 49)		
CYCLE1_DAY15	5960 (± 999999)	2683 (± 65)		
CYCLE2_DAY1	8620 (± 999999)	2753 (± 999999)		
CYCLE3_DAY1	999999 (± 999999)	1520 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) for Avelumab

End point title	Maximum Observed Plasma Concentration (Cmax) for Avelumab[4]

End point description:

Cmax was the maximum observed plasma concentration and was directly observed from data. The LLQ was 0.20 microgram per milliliter. Concentration values below the LLQ were set to zero. Geometric Mean analysis was on the log scale. Zero values were not included in geometric mean and geometric coefficient of variation calculation. The geometric coefficient of variation is expressed in percentage. Number of subjects that started the Arm: subjects who had at least 1 concentration measurement for avelumab. Therefore, only 2 treatment groups including avelumab were analyzed. Number of Subjects Analyzed: subjects who had avelumab concentrations above the LLQ at specific time point.

End point type	Secondary

End point timeframe:

Post dose on Day 1 and Day 15 of Cycle 1 (each cycle is 28 days); Day 1 and Day 15 of Cycle 2; and Day 1 of Cycles 3, 5, 9 and 12.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis was planned only for the arms specified.

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: microgram per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
CYCLE1_DAY1	205.3 (± 22)	248.6 (± 14)		
CYCLE1_DAY15	214.2 (± 20)	237.4 (± 45)		
CYCLE2_DAY1	213.0 (± 20)	241.5 (± 26)		
CYCLE2_DAY15	211.5 (± 17)	243.0 (± 19)		
CYCLE3_DAY1	176.0 (± 999999)	233.7 (± 28)		

CYCLE5_DAY1	188.0 (± 999999)	241.9 (± 21)		
CYCLE9_DAY1	999999 (± 999999)	257.0 (± 999999)		
CYCLE12_DAY1	999999 (± 999999)	255.8 (± 999999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) for Binimetinib

End point title	Maximum Observed Plasma Concentration (Cmax) for Binimetinib

End point description:

Cmax was the maximum observed plasma concentration and was directly observed from data. The LLQ was 1.00 ng/mL. Concentration values below the LLQ were set to zero. Geometric Mean analysis was on the log scale. Zero values were not included in geometric mean and geometric coefficient of variation calculation. The geometric coefficient of variation is expressed in percentage. When Cmax for binimetinib was planned to be evaluated, data collecting for Avelumab+Binimetinib cohort had already been done. Therefore, data of Cmax for binimetinib in Avelumab+Binimetinib groups hadn't been collected. Number of subjects that started the Arm: subjects who had at least 1 concentration measurement for binimetinib. Number of Subjects Analyzed: subjects who had binimetinib concentrations above the LLQ at specific time point.

End point type	Secondary

End point timeframe:

Post dose on Day 1 and Day 8 of Cycle 1

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[5]	0[6]	7	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
CYCLE1_DAY1	()	()	370.24 (± 64)	331.74 (± 63)
CYCLE1_DAY8	()	()	183.53 (± 180)	446.81 (± 59)

Notes:

[5] - Data of Cmax for binimetinib in Avelumab+Binimetinib groups hadn't been collected

[6] - Data of Cmax for binimetinib in Avelumab+Binimetinib groups hadn't been collected

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With anti-drug antibody (ADA) Categories

End point title	Number of Subjects With anti-drug antibody (ADA)

End point description:

Blood samples were collected for avelumab immunogenicity testing. Samples positive for ADA were

analyzed for titer. Treatment-boosted ADA was defined as a positive ADA result at baseline and the titer ≥ 8×baseline titer at least once after treatment with avelumab. Treatment-induced ADA was defined as subjects with ADA-negative at baseline and had at least one positive post-baseline ADA result; or if subject did not have a baseline sample, the subject had at least one positive post-baseline ADA result. Subjects in the safety analysis set had at least one ADA/nAb sample collected for avelumab, so only two groups (Avelumab+Binimetinib 30mg [Phase 1b] and Avelumab+Binimetinib 45mg [Phase 1b]) were analyzed.

End point type	Secondary

End point timeframe:

From the first dose of study up to Day 1 of Cycle 12 for a maximum of 12 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned only for the arms specified.

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: Subjects				
ADA never-positive	8	11		
ADA ever-positive	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Neutralizing Antibodies (nAb) Against Avelumab

End point title	Neutralizing Antibodies (nAb) Against Avelumab[8]

End point description:

The category of nAb included nAb never-positive, nAb ever-positive, baseline nAb positive, treatment-induced nAb, transient nAb response and persistent nAb response. Subjects in the safety analysis set had at least one ADA/nAb sample collected for avelumab; however, due to the low observed immunogenicity rate, nAb analysis was not conducted.

End point type	Secondary

End point timeframe:

From the first dose of study up to Day 1 of Cycle 12 for a maximum of 12 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Analysis was planned only for the arms specified.

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Subjects				

Notes:

[9] - nAb analysis was not conducted.

[10] - nAb analysis was not conducted.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Confirmed Objective Response (OR) in Phase 1b Based on Investigator Assessment (RECIST v1.1)

End point title	Percentage of Subjects With Confirmed Objective Response (OR) in Phase 1b Based on Investigator Assessment (RECIST v1.1)

End point description:

OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the 'start date' (date of first study treatment) until the date of the first documentation of progressive disease (PD). CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. PD was defined as a 20% increase in the sum of diameters of target lesions or unequivocal progression of non-target lesions or the appearance of any new malignant lesion. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. Clopper-Pearson method was used. The full analysis set included all enrolled subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From date of first study treatment until the date of first documentation of progressive disease or death due to any cause (assessed for a maximum duration of up to 31 months).

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	7	6
Units: Percentage of subjects				
number (confidence interval 95%)	0 (0.0 to 30.8)	8.3 (0.2 to 38.5)	0 (0.0 to 41.0)	0 (0.0 to 45.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Based on Investigator Assessment (RECIST v1.1) in Phase 1b

End point title	Progression-Free Survival (PFS) Based on Investigator Assessment (RECIST v1.1) in Phase 1b

End point description:

PFS is defined as the time from the 'start date' (date of first study treatment) to the date of the first documentation of PD or death due to any cause, whichever occurs first. PD was defined as a 20% increase in the sum of diameters of target lesions or unequivocal progression of non-target lesions or the appearance of any new malignant lesion. CIs were calculated using Brookmeyer and Crowley method. The full analysis set included all enrolled subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From date of first study treatment until the date of first documentation of progressive disease or death

due to any cause (assessed for a maximum duration of up to 31 months).

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	7	6
Units: months				
median (confidence interval 95%)	1.7 (1.6 to 2.9)	3.3 (1.6 to 7.1)	1.6 (1.0 to 2.3)	1.8 (1.1 to 4.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Phase 1b

End point title	Overall Survival (OS) in Phase 1b

End point description:

OS is defined as the time from the 'start date' (date of first study treatment) to the date of death due to any cause. CIs were calculated using Brookmeyer and Crowley method. The full analysis set included all enrolled subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

From date of first study treatment until the date of death due to any cause (assessed for a maximum duration of up to 31 months).

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	12	7	6
Units: months				
median (confidence interval 95%)	5.9 (2.9 to 8.6)	8.0 (3.0 to 20.1)	2.9 (1.0 to 999999)	10.7 (1.1 to 10.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Tumor Response (TTR) in Phase 1b

End point title	Time-to-Tumor Response (TTR) in Phase 1b

End point description:

TTR is defined, for subjects with an OR, as the time from the date of first study treatment to the first

documentation of objective response (CR or PR) which was subsequently confirmed. OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the 'start date' until the date of the first documentation of progressive disease (PD). CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. Subjects who received at least 1 dose of study treatment and achieved objective response were analyzed: only 1 subject in the Avelumab+Binimetinib 45mg (Phase 1b) group achieved OR. The summary of this endpoint cannot be estimated due to small sample size (1 subject).

End point type	Secondary

End point timeframe:

From date of first study treatment until the date of first documentation of progressive disease or death due to any cause (assessed for a maximum duration of up to 31 months).

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[11]	0[12]	0[13]	0[14]
Units: months				
median (full range (min-max))	(to)	(to)	(to)	(to)

Notes:

[11] - There is no subject achieved OR.

[12] - Only one subject achieved OR.

[13] - There is no subject achieved OR.

[14] - There is no subject achieved OR.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR) in Phase 1b

End point title	Duration of Response (DR) in Phase 1b

End point description:

DR is defined, for subjects with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause. OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the 'start date' until the date of the first documentation of progressive disease (PD). CR was defined as complete disappearance of all target and non-target lesions, with the exception of nodal disease and sustained for at least 4 weeks. PR was defined as at least 30% decrease in the sum of the longest dimensions of target lesions taking as reference the baseline sum longest dimensions. The full analysis set included all enrolled subjects who received at least 1 dose of study treatment and achieved objective response: only 1 subject in the Avelumab+Binimetinib 45mg (Phase 1b) group achieved OR. The summary of this endpoint cannot be estimated due to small sample size (1 subject).

End point type	Secondary

End point timeframe:

From date of first study treatment until the date of first documentation of progressive disease or death due to any cause (assessed for a maximum duration of up to 31 months).

End point values	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[15]	0[16]	0[17]	0[18]
Units: months				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[15] - There is no subject achieved OR.

[16] - Only one subject achieved OR.

[17] - There is no subject achieved OR.

[18] - There is no subject achieved OR.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day) assessed for a maximum duration of up to 31 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Avelumab+Binimetinib 30mg (Phase 1b)

Reporting group description:

Avelumab was administered at a fixed dose of 800 mg Q2W in combination with binimetinib at 30 mg BID orally on a continuous daily dosing schedule.

Reporting group title	Avelumab+Binimetinib 45mg (Phase 1b)

Reporting group description:

Avelumab was administered at a fixed dose of 800 mg Q2W in combination with binimetinib at 45 mg BID orally on a continuous daily dosing schedule.

Reporting group title	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)

Reporting group description:

Binimetinib 30 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.

Reporting group title	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)

Reporting group description:

Binimetinib 45 mg was administered orally BID (7 days on / 7 days off) with talazoparib at 0.75 mg once daily (QD) orally on a continuous dosing schedule.

Serious adverse events	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	9 / 12 (75.00%)	3 / 7 (42.86%)
number of deaths (all causes)	9	9	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (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
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (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
Embolism			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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			
Chills			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (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
Disease progression			
subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Mucosal inflammation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Skin laceration			

subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (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
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			

subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (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

Serious adverse events	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				

Alanine aminotransferase increased				
subjects affected / exposed	0 / 6 (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 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial infarction				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Encephalopathy				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Ascites				

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hyperbilirubinaemia				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Avelumab+Binimetinib 30mg (Phase 1b)	Avelumab+Binimetinib 45mg (Phase 1b)	Binimetinib 30mg+Talazoparib 0.75mg (Phase 1b)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	12 / 12 (100.00%)	7 / 7 (100.00%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Diastolic hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Embolism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Haematoma			

subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	4 / 12 (33.33%)	0 / 7 (0.00%)
occurrences (all)	1	6	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 10 (20.00%)	4 / 12 (33.33%)	4 / 7 (57.14%)
occurrences (all)	3	5	7
Mucosal inflammation			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	4	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	4 / 12 (33.33%)	1 / 7 (14.29%)
occurrences (all)	1	6	1
Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	4	2	2
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Hypoxia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Investigations			

Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 10 (40.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	7	4	0
Ammonia increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 10 (50.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	10	3	0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	5	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 10 (30.00%)	4 / 12 (33.33%)	3 / 7 (42.86%)
occurrences (all)	9	16	4
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)	1 / 7 (14.29%)
occurrences (all)	0	4	1
Ejection fraction decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
International normalised ratio increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Lipase increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	4
Troponin T increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eye contusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Infusion related reaction			
subjects affected / exposed	3 / 10 (30.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	3	1	0
Skin wound			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Burning sensation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Tension headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)	2 / 7 (28.57%)
occurrences (all)	0	5	3
Iron deficiency anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Leukocytosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Dry eye			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Glaucoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Macular oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Periorbital oedema			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Photopsia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Subretinal fluid			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	3 / 10 (30.00%)	2 / 12 (16.67%)	1 / 7 (14.29%)
occurrences (all)	6	3	1
Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Ascites			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Cheilitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	2	2	1
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	4 / 12 (33.33%)	2 / 7 (28.57%)
occurrences (all)	3	6	4
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Lip blister			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 10 (20.00%)	4 / 12 (33.33%)	3 / 7 (42.86%)
occurrences (all)	2	4	4
Obstruction gastric			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

Retching			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 10 (30.00%)	4 / 12 (33.33%)	4 / 7 (57.14%)
occurrences (all)	3	6	6
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	4 / 10 (40.00%)	3 / 12 (25.00%)	2 / 7 (28.57%)
occurrences (all)	8	3	2
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Erythema multiforme			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	2 / 10 (20.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	3	2	0
Rash			
subjects affected / exposed	5 / 10 (50.00%)	7 / 12 (58.33%)	2 / 7 (28.57%)
occurrences (all)	5	11	2
Rash maculo-papular			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Flank pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Coccydynia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nail infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Rash pustular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	4	0
Sinusitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Wound infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Dehydration			
subjects affected / exposed	2 / 10 (20.00%)	2 / 12 (16.67%)	2 / 7 (28.57%)
occurrences (all)	2	2	2
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hyperphosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 12 (16.67%)	0 / 7 (0.00%)
occurrences (all)	3	4	0

Hypocalcaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Hypokalaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	5
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	7	0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Binimetinib 45mg+Talazoparib 0.75mg (Phase 1b)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Diastolic hypertension			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Embolism			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypertension			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	6		
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory tract congestion			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Upper-airway cough syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Investigations			
Activated partial thromboplastin time prolonged			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Alanine aminotransferase increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Ammonia increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Ejection fraction decreased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Fibrin D dimer increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
International normalised ratio increased				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lipase increased				

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	4		
Troponin T increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Eye contusion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Infusion related reaction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin wound			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Burning sensation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Dizziness subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Dysgeusia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Sciatica subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Tension headache subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Tremor subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Leukocytosis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Eye disorders			

Cataract subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Detachment of retinal pigment epithelium subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Dry eye subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Glaucoma subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Macular oedema subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Periorbital oedema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Photopsia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Retinopathy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Subretinal fluid subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vision blurred subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Gastrointestinal disorders			

Abdominal discomfort				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Abdominal pain				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences (all)	1			
Abdominal pain upper				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Ascites				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Cheilitis				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Constipation				
subjects affected / exposed	2 / 6 (33.33%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	3 / 6 (50.00%)			
occurrences (all)	4			
Dry mouth				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Lip blister				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			
Nausea				
subjects affected / exposed	4 / 6 (66.67%)			
occurrences (all)	5			
Obstruction gastric				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences (all)	0			

Retching subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Toothache subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vomiting subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3		
Hepatobiliary disorders			
Hepatic pain subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 8		
Dry skin subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Erythema subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Erythema multiforme subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Rash subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Coccydynia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Clostridium difficile infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nail infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Oral candidiasis			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash pustular			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Wound infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2		
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Vitamin B12 deficiency subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2019	1. Due to dose-limiting toxicities seen with the doublet of avelumab and continuous daily binimetib dosing, the study design has been updated. 2. Phase 2 design has been modified to remove the randomized NSCLC cohort due to enrollment concerns. This tumor agnostic cohort was also increased in size from 20 to 30 subjects to accommodate this change. 3. The study title, schedule of activities, protocol background section, study objectives and endpoints, inclusion and exclusion criteria, assessments (Section 7) and references have been updated. 4. The maximum administered dose definition has been updated to reflect the intermittent schedule of binimetinib and the modified doublet combination of binimetinib and talazoparib. 5. Section 5.5 has been updated to clarify the treatment administration procedures to be followed due to the updated study design. 6. The dose-limiting toxicity definitions have been updated to align with visit scheduling and the current guidance for binimetinib protocols. 7. The dose modification guidance has been updated to improve consistency and align with the guidance in the prescribing information and current protocol guidance for binimetinib, talazoparib and avelumab. 8. Section 5.8.3 has been updated to clarify requirements for use of steroids in the management of treatment-related adverse events. 9. Sections 5.8.6 and 5.8.7 have been updated based on current guidance for prohibited medications. 10. Section 6.4 has been updated to clarify that all subjects are expected to enter survival follow-up, even if they discontinue short-term follow-up prior to completing the 90 day follow-up period. 11. Section 8.3 has been updated to remove Grade 0 from the 'Clinical Description of Severity' table. 12. The statistical sections of the protocol (Section 9) was updated to reflect the changes in study design, including the addition of Appendix 6.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 March 2020	COVID-19 pandemic was occurring globally. When the pandemic occurred, the study recruitment was temporarily paused from 24 March 2020 to 03 May 2020. The objectives of the study were not affected by the pandemic and the impact was minimal.	04 May 2020

Notes:

Limitations and caveats

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

A decision on early termination of this study was made on 14 Dec 2020. Due to this, only the doublet combinations in Phase 1b to find a safe dose were conducted. Due to the low observed immunogenicity rate, nAb analysis was not conducted.

Notes: