Clinical trial results:
Phase Ib/II Study of Cobimetinib Administered as Single Agent and in Combination with Venetoclax, with or without Atezolizumab, in Patients with Relapsed and Refractory Multiple Myeloma.

Summary

EudraCT number	2017-000830-68
Trial protocol	NL DK SE DE CZ ES FR PL
Global end of trial date	18 May 2021

Results information

Result version number	v1
This version publication date	27 May 2022
First version publication date	27 May 2022

Trial information

Trial identification

Sponsor protocol code	BO39813

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03312530
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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	18 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 May 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to evaluate the efficacy, safety, tolerability, and pharmacokinetics of cobimetinib administered as a single agent, cobimetinib plus venetoclax, and cobimetinib plus venetoclax plus atezolizumab in patients with Relapsed and Refractory Multiple Myeloma (R/R MM).

Protection of trial subjects:

All study subjects were required to read and sign and Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Norway: 18
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	22
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 16 centers in 8 countries.

Pre-assignment

Screening details:

A total of 62 participants were screend, of which 49 participants were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-In: Cobimetinib + Venetoclax

Arm description:

Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses, in 28-day cycles, to identify the dose level with acceptable safety.

Arm type	Experimental
Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered PO daily at a dose of 40 mg on Days 1-21.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was administered PO daily at a dose of 800 mg on Days 1-28.

Arm title	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab

Arm description:

Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses and atezolizumab (on Day 1 and Day 15) at a fixed dose of 840 mg IV, in 28-day cycles, to identify the dose level with acceptable safety.

Arm type	Experimental
Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered PO daily at a dose of 40 mg on Days 1-21.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab was administered by IV infusion at a dose of 840 mg on Days 1 and 15.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was administered PO daily at a dose of 800 mg on Days 1-28.

Arm title	A: Cobimetinib

Arm description:

Participants received the standard single-agent cobimetinib dose of 60 milligrams (mg) (3 tablets of 20 mg each) orally (PO) daily on Days 1-21 of each 28-day cycle until disease progression. Upon progression, participants were allowed to receive treatment with cobimetinib and atezolizumab at the recommended Phase II dose of cobimetinib 60 mg PO on Days 1-21 plus atezolizumab intravenous (IV) infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered PO daily at a dose of 60 mg on Days 1-21.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab was administered by IV infusion at a dose of 840 mg on Days 1 and 15.

Arm title	B: Cobimetinib + Venetoclax

Arm description:

Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered PO daily at a dose of 40 mg on Days 1-21.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was administered PO daily at a dose of 800 mg on Days 1-28.

Arm title	C: Cobimetinib + Venetoclax + Atezolizumab

Arm description:

Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase plus atezolizumab IV infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Cobimetinib
Investigational medicinal product code	
Other name	Cotellic
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Cobimetinib was administered PO daily at a dose of 40 mg on Days 1-21.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Atezolizumab was administered by IV infusion at a dose of 840 mg on Days 1 and 15.

Investigational medicinal product name	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was administered PO daily at a dose of 800 mg on Days 1-28.

Number of subjects in period 1	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib
Started	6	6	6
Completed	0	0	0
Not completed	6	6	6
Consent withdrawn by subject	-	1	-
Death	5	5	4
Study terminated by sponsor	1	-	2
Summarized as 'ongoing' due to missing data entry	-	-	-

Lost to follow-up	-	-	-
Participant in another sponsor study	-	-	-

Number of subjects in period 1	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab
Started	16	15
Completed	0	0
Not completed	16	15
Consent withdrawn by subject	-	-
Death	10	8
Study terminated by sponsor	3	7
Summarized as 'ongoing' due to missing data entry	1	-
Lost to follow-up	1	-
Participant in another sponsor study	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Safety Run-In: Cobimetinib + Venetoclax
Reporting group description:	
Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses, in 28-day cycles, to identify the dose level with acceptable safety.	
Reporting group title	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab
Reporting group description:	
Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses and atezolizumab (on Day 1 and Day 15) at a fixed dose of 840 mg IV, in 28-day cycles, to identify the dose level with acceptable safety.	
Reporting group title	A: Cobimetinib
Reporting group description:	
Participants received the standard single-agent cobimetinib dose of 60 milligrams (mg) (3 tablets of 20 mg each) orally (PO) daily on Days 1-21 of each 28-day cycle until disease progression. Upon progression, participants were allowed to receive treatment with cobimetinib and atezolizumab at the recommended Phase II dose of cobimetinib 60 mg PO on Days 1-21 plus atezolizumab intravenous (IV) infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.	
Reporting group title	B: Cobimetinib + Venetoclax
Reporting group description:	
Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.	
Reporting group title	C: Cobimetinib + Venetoclax + Atezolizumab
Reporting group description:	
Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase plus atezolizumab IV infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.	

Reporting group values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib
Number of subjects	6	6	6
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)	2	2	1
From 65-84 years	4	4	5
85 years and over	0	0	0

Age Continuous Units: years			
arithmetic mean	65.8	66.5	68.0
standard deviation	± 7.6	± 6.1	± 5.9
Gender Categorical Units: Subjects			
Female	4	3	2
Male	2	3	4
Race/Ethnicity, Customized Units: Subjects			
White	6	6	6
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	6	6
Not Stated	0	0	0
Unknown	0	0	0

Reporting group values	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab	Total
Number of subjects	16	15	49
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)	7	10	22
From 65-84 years	9	5	27
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	64.1	61.5	
standard deviation	± 6.0	± 10.5	-
Gender Categorical Units: Subjects			
Female	6	3	18
Male	10	12	31
Race/Ethnicity, Customized Units: Subjects			
White	16	15	49
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	14	11	43
Not Stated	1	2	3
Unknown	0	1	1

End points

End points reporting groups

Reporting group title	Safety Run-In: Cobimetinib + Venetoclax
Reporting group description:	
Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses, in 28-day cycles, to identify the dose level with acceptable safety.	
Reporting group title	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab
Reporting group description:	
Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses and atezolizumab (on Day 1 and Day 15) at a fixed dose of 840 mg IV, in 28-day cycles, to identify the dose level with acceptable safety.	
Reporting group title	A: Cobimetinib
Reporting group description:	
Participants received the standard single-agent cobimetinib dose of 60 milligrams (mg) (3 tablets of 20 mg each) orally (PO) daily on Days 1-21 of each 28-day cycle until disease progression. Upon progression, participants were allowed to receive treatment with cobimetinib and atezolizumab at the recommended Phase II dose of cobimetinib 60 mg PO on Days 1-21 plus atezolizumab intravenous (IV) infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.	
Reporting group title	B: Cobimetinib + Venetoclax
Reporting group description:	
Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.	
Reporting group title	C: Cobimetinib + Venetoclax + Atezolizumab
Reporting group description:	
Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase plus atezolizumab IV infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.	

Primary: Percentage of Participants With Adverse Events (AEs)

End point title	Percentage of Participants With Adverse Events (AEs)[1]
End point description:	
An AE was any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with the treatment. An AE was therefore any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. New or pre-existing conditions which worsened during the study were also considered AEs. The safety evaluable population included all participants who received any amount of study drug.	
End point type	Primary
End point timeframe:	
Randomization up to end of study (up to approximately 3 years, 7 months)	

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: No statistical analyses provided as no formal hypothesis testing was planned for this study.

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	16
Units: Percentage of Participants				
number (not applicable)	100.0	100.0	100.0	100.0

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Percentage of Participants				
number (not applicable)	100.0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Overall Response Rate (ORR) as Determined by the Investigator Using International Myeloma Working Group (IMWG) Response Criteria

End point title	Percentage of Participants With Overall Response Rate (ORR) as Determined by the Investigator Using International Myeloma Working Group (IMWG) Response Criteria[2]

End point description:

ORR was defined as a stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) and was analyzed in the safety evaluable population and in the biomarker-selected sub-populations of t(11;14) and RAS mutations. The safety evaluable population included all participants who received any amount of study drug. 9999 to 9999999 = no participants were included in the t(11;14) biomarker-selected population within this arm.

End point type	Primary

End point timeframe:

From randomization to the first occurrence of disease progression or relapse or death from any cause, whichever occurs first (up to approximately 3 years, 7 months).

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: No statistical analyses provided as no formal hypothesis testing was planned for this study.

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	16
Units: Percentage of Participants				
number (confidence interval 95%)				
Safety Population (n=6,6,6,16,15)	16.7 (0.00 to 54.82)	33.3 (0.00 to 79.39)	0 (0.00 to 8.33)	31.3 (5.41 to 57.09)

t(11;14) Population (n=0,1,1,2,5)	99999 (9999 to 9999999)	100 (50.00 to 100.00)	0 (0.00 to 50.00)	100 (75.00 to 100.00)
RAS Mutation Population (n=2,1,2,7,8)	0 (0.00 to 25.00)	100 (50.00 to 100.00)	0 (0.00 to 25.00)	14.3 (0.00 to 47.35)

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Percentage of Participants				
number (confidence interval 95%)				
Safety Population (n=6,6,6,16,15)	26.7 (0.95 to 52.38)			
t(11;14) Population (n=0,1,1,2,5)	80.0 (34.94 to 100.00)			
RAS Mutation Population (n=2,1,2,7,8)	37.5 (0.00 to 77.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinical Benefit as Determined by the Investigator Using IMWG Response Criteria

End point title	Percentage of Participants With Clinical Benefit as Determined by the Investigator Using IMWG Response Criteria

End point description:

Clinical benefit rate (CBR) was defined as a minimal response (MR) or better (PR,VGPR, CR, sCR). The safety evaluable population included all participants who received any amount of study drug.

End point type	Secondary

End point timeframe:

From randomization to the first occurrence of a response as defined above (up to approximately 3 years, 7 months)

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	16
Units: Percentage of Participants				
number (confidence interval 95%)	33.3 (0.00 to 79.39)	33.3 (0.00 to 79.39)	0 (0.00 to 8.33)	43.8 (16.32 to 71.18)

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Percentage of Participants				
number (confidence interval 95%)	33.3 (6.14 to 60.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) as Determined by the Investigator Using IMWG Response Criteria

End point title	Progression-Free Survival (PFS) as Determined by the Investigator Using IMWG Response Criteria

End point description:

PFS was defined as the time from randomization (for randomized participants) or first treatment date (for non-ranomized participants) to the first occurrence of disease progression or relapse as determined by the investigator using the IMWG criteria or death from any cause during the study, whichever occurred first. The safety evaluable population included all participants who received any amount of study drug.

End point type	Secondary

End point timeframe:

From enrollment or first treatment date to the first occurrence of disease progression or relapse or death from any cause, whichever occurs first (up to approximately 3 years, 7 months)

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	16
Units: Months				
median (confidence interval 95%)	1.7 (0.9 to 3.7)	3.4 (2.1 to 4.6)	2.8 (1.9 to 4.7)	4.9 (1.9 to 10.3)

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	3.8 (1.4 to 4.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Determined by the Investigator Using IMWG Response Criteria

End point title	Duration of Response (DOR) as Determined by the Investigator Using IMWG Response Criteria[3]

End point description:

DOR was applicable to participants who achieved at least a PR, and was measured from the first observation of PR or better to the time of disease progression. The safety evaluable population included all participants who received any amount of study drug.
9999999 = not estimable, could not be calculated due to too few events.
9.999999 to 9999999 = the 95% CI could not be calculated from the data of one participant.

End point type	Secondary

End point timeframe:

Time from the first observation of partial response (PR) to the time of disease progression (up to approximately 3 years, 7 months).

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: In Arm A, there were no participants who achieved a response and hence why that arm is not presented.

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	5	4
Units: Months				
median (confidence interval 95%)	11.5 (9.999999 to 9999999)	4.9 (2.3 to 9999999)	15.2 (1.9 to 9999999)	999999 (1.9 to 99999999)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization until death from any cause. The safety evaluable population included all participants who received any amount of study drug. 9999999 = not estimable, could not be calculated due to too few events.

End point type	Secondary

End point timeframe:

From randomization until death from any cause (up to approximately 3 years, 7 months).

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	16
Units: Months				
median (confidence interval 95%)	11.4 (6.3 to 13.9)	14.3 (14.1 to 9999999)	12.9 (3.2 to 9999999)	13.5 (8.0 to 26.9)

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	22.0 (15.5 to 9999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve (AUC) of Cobimetinib

End point title	Area Under the Plasma Concentration Versus Time Curve (AUC) of Cobimetinib

End point description:

AUC0-24hr area under the plasma concentration-time curve from time 0 to 24 hrs. The PK population included participants from Arms A, B, and C who received at least one dose of study medication and for whom at least one evaluable PK sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hr), 2, 4, 6 hrs post-dose on Day 15 of Cycle 1 (cycle length: 28 days)

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	0[4]	11
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	2390 (± 53.4)	3190 (± 55.3)	()	2540 (± 78.1)

Notes:

[4] - No PK parameters were calculated due to limited sampling times.

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	2900 (± 54.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Cobimetinib

End point title	Maximum Observed Plasma Concentration (Cmax) of Cobimetinib

End point description:

Cmax is the maximum observed plasma concentration at steady state. The PK population included participants from Arms A, B, and C who received at least one dose of study medication and for whom at least one evaluable PK sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hr), 2, 4, 6 hrs post-dose on Day 15 of Cycle 1 (cycle length: 28 days)

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	0[5]	13
Units: ng/mL				
geometric mean (geometric coefficient of variation)	157 (± 63.5)	192 (± 61.7)	()	148 (± 72.6)

Notes:

[5] - No PK parameters were calculated due to limited sampling times

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	166 (± 61.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (Tmax) of Cobimetinib

End point title	Time to Reach Cmax (Tmax) of Cobimetinib

End point description:

Tmax is the time to reach Cmax. The PK population included participants from Arms A, B, and C who received at least one dose of study medication and for whom at least one evaluable PK sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hr), 2, 4, 6 hrs post-dose on Day 15 of Cycle 1 (cycle length: 28 days)

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	A: Cobimetinib	B: Cobimetinib + Venetoclax
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	0[6]	13
Units: hr				
median (full range (min-max))	4.00 (2.10 to 4.02)	4.00 (2.05 to 5.73)	(to)	4.00 (2.00 to 6.08)

Notes:

[6] - No PK parameters were calculated due to limited sampling times.

End point values	C: Cobimetinib + Venetoclax + Atezolizumab			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: hr				
median (full range (min-max))	4.00 (2.23 to 6.37)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of Venetoclax

End point title	AUClast of Venetoclax[7]

End point description:

AUClast=area under the plasma concentration-time curve (samples collected to 8hr postdose on C1D15). The PK population included participants from Arms B and C who received at least one dose of study medication and for whom at least one evaluable PK sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hr), 2, 4, 6, 8 hrs post-dose on Day 15 of Cycle 1 (cycle length: 28 days)

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: This analysis was only performed on the arms with Venetoclax and hence why not all arms are presented.

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	13	11
Units: hr*ug/mL				
geometric mean (geometric coefficient of variation)	4.96 (± 67.2)	5.13 (± 57.0)	6.52 (± 63.7)	6.52 (± 51.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Venetoclax

End point title	Cmax of Venetoclax[8]

End point description:

Cmax is the maximum observed plasma concentration at steady state. The PK population included participants from Arms B and C who received at least one dose of study medication and for whom at least one evaluable PK sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hr), 2, 4, 6, 8 hrs post-dose on Day 15 of Cycle 1 (cycle length: 28 days)

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: This analysis was only performed on the arms with Venetoclax and hence why not all arms are presented.

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	13	11
Units: ug/mL				
geometric mean (geometric coefficient of variation)	1.25 (± 81.0)	1.16 (± 48.7)	1.32 (± 55.3)	1.35 (± 18.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Venetoclax

End point title	Tmax of Venetoclax[9]

End point description:

Tmax is the time to reach Cmax. The PK population included participants from Arms B and C who received at least one dose of study medication and for whom at least one evaluable PK sample was collected.

End point type	Secondary

End point timeframe:

Pre-dose (within 1 hr), 2, 4, 6, 8 hrs post-dose on Day 15 of Cycle 1 (cycle length: 28 days)

Notes:

[9] - 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: This analysis was only performed on the arms with Venetoclax and hence why not all arms are presented.

End point values	Safety Run-In: Cobimetinib + Venetoclax	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	5	13	11
Units: hr				
median (full range (min-max))	5.73 (3.92 to 5.77)	5.65 (3.75 to 5.78)	6.00 (3.95 to 8.50)	5.92 (0 to 8.17)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-Drug Antibody (ADA) to Atezolizumab

End point title	Percentage of Participants With Anti-Drug Antibody (ADA) to Atezolizumab[10]

End point description:

The immunogenicity analysis population for atezolizumab consisted of all participants from Arm C with any ADA assessment.

End point type	Secondary

End point timeframe:

Pre-infusion (0 hr) on Day 1 of Cycles 1, 2, 3 (cycle length: 28 days); at treatment discontinuation visit (up to approximately 3 years, 7 months)

Notes:

[10] - 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: This analysis was only performed on the arms with Atezolizumab and hence why not all arms are presented.

End point values	Safety Run-In: Cobimetinib + Venetoclax + Atezolizumab	C: Cobimetinib + Venetoclax + Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	14		
Units: Percentage of Participants				
number (not applicable)	50.0	28.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization up to end of study (up to approximately 3 years, 7 months)

Adverse event reporting additional description:

AEs were recorded for the safety-evaluable population, which included all participants who received any amount of study drug and analyzed according to the treatment arm they received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Safety Run-In: Cobimetinib+Venetoclax

Reporting group description:

Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses, in 28-day cycles, to identify the dose level with acceptable safety.

Reporting group title	Safety Run-In: Cobimetinib+Venetoclax+Atezolizumab

Reporting group description:

Participants received cobimetinib (on Day 1-21) plus venetoclax (on Day 1-28) at escalated doses and atezolizumab (on Day 1 and Day 15) at a fixed dose of 840 mg IV, in 28-day cycles, to identify the dose level with acceptable safety.

Reporting group title	A: Cobimetinib

Reporting group description:

Participants received the standard single-agent cobimetinib dose of 60 milligrams (mg) (3 tablets of 20 mg each) orally (PO) daily on Days 1-21 of each 28-day cycle until disease progression. Upon progression, participants were allowed to receive treatment with cobimetinib and atezolizumab at the recommended Phase II dose of cobimetinib 60 mg PO on Days 1-21 plus atezolizumab intravenous (IV) infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.

Reporting group title	B: Cobimetinib + Venetoclax

Reporting group description:

Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.

Reporting group title	C: Cobimetinib + Venetoclax + Atezolizumab

Reporting group description:

Participants received cobimetinib PO daily on Days 1-21 of each 28-day cycle plus venetoclax PO daily on Days 1-28 of each 28-day cycle, at the dose level identified in the safety run-in phase plus atezolizumab IV infusion at a fixed dose of 840 mg on Day 1 and Day 15 of each 28-day cycle. Treatment continued until disease progression, unacceptable toxicity, death, participant or physician decision to withdraw, or pregnancy, whichever occurred first.

Serious adverse events	Safety Run-In: Cobimetinib+Venetoclax	Safety Run-In: Cobimetinib+Venetoclax+Atezolizumab	A: Cobimetinib
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	3 / 6 (50.00%)	3 / 6 (50.00%)
number of deaths (all causes)	5	4	4
number of deaths resulting from adverse events	0	0	0

Investigations			
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIROVIRUS TEST POSITIVE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGIC STROKE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
SYNCOPE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (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
Gastrointestinal disorders			
VOMITING			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL ULCER			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
NECK PAIN			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
INTERVERTEBRAL DISCITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTATE INFECTION			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LISTERIA SEPSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PNEUMOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA PNEUMOCOCCAL			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORAL HERPES			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPHILUS SEPSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
HYPONATRAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOKALAEMIA			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)	11 / 15 (73.33%)	
number of deaths (all causes)	11	8	
number of deaths resulting from adverse events	0	1	
Investigations			
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIROVIRUS TEST POSITIVE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC STROKE			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PYREXIA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
VOMITING			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL ULCER			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
NECK PAIN			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
INTERVERTEBRAL DISCITIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LISTERIA SEPSIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PNEUMONIA			
subjects affected / exposed	4 / 16 (25.00%)	2 / 15 (13.33%)	
occurrences causally related to treatment / all	2 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCOCCAL BACTERAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL HERPES			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOPHILUS SEPSIS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			

subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPONATRAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR LYSIS SYNDROME			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Run-In: Cobimetinib+Venetoclax	Safety Run-In: Cobimetinib+Venetoclax+Atezolizumab	A: Cobimetinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	6 / 6 (100.00%)	5 / 6 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
ADENOCARCINOMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			

ESSENTIAL HYPERTENSION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HAEMATOMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
HYPERTENSION			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
PERIPHERAL VENOUS DISEASE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
PYREXIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
FEELING COLD			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
FACE OEDEMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
FATIGUE			
subjects affected / exposed	4 / 6 (66.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	5	1	0
ASTHENIA			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
CHEST PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 6 (33.33%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
BALANOPOSTHITIS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DYSPNOEA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
EPISTAXIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
SINUS PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
COUGH			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
BLOOD POTASSIUM DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
VITAMIN B12 DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
INFLUENZA A VIRUS TEST POSITIVE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	3 / 6 (50.00%)	3 / 6 (50.00%)	1 / 6 (16.67%)
occurrences (all)	3	3	1
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
EJECTION FRACTION DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
WEIGHT DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
TROPONIN T INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
BLOOD CREATINE INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HAEMOGLOBIN DECREASED			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
TROPONIN INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
LIPASE INCREASED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
BLOOD URIC ACID INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
AMYLASE INCREASED			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
BLOOD CALCIUM INCREASED			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
EYE CONTUSION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
FALL			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
ATRIOVENTRICULAR BLOCK			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
CARDIAC FAILURE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
NEURALGIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
SYNCOPE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
DYSGEUSIA			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
PARAESTHESIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
SCIATICA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPERSOMNIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
DYSAESTHESIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
AUTONOMIC NEUROPATHY			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
POST HERPETIC NEURALGIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HEADACHE			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	3	0	0
HYPERAESTHESIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
HYPOAESTHESIA			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
LYMPHOPENIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

NEUTROPENIA			
subjects affected / exposed	3 / 6 (50.00%)	4 / 6 (66.67%)	0 / 6 (0.00%)
occurrences (all)	4	10	0
ANAEMIA			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
PANCYTOPENIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
LEUKOPENIA			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
HAEMORRHAGIC DIATHESIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
VERTIGO			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
EYE HAEMORRHAGE			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DETACHMENT OF RETINAL PIGMENT EPITHELIUM			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
RETINAL HAEMORRHAGE			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
OPTIC NERVE CUPPING			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DRY EYE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PHOTOPHOBIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
SWELLING OF EYELID			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
SUBRETINAL FLUID			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
BLEPHAROCHALASIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
CHALAZION			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
BLEPHARITIS			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
DYSPHAGIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
GASTROOESOPHAGEAL REFLUX DISEASE			

subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
MELAENA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
CONSTIPATION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	3
VOMITING			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
FLATULENCE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
ORAL PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
DRY MOUTH			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
FAECES DISCOLOURED			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
HAEMATEMESIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
STOMATITIS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
GASTROINTESTINAL PAIN			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
ANORECTAL DISCOMFORT			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HAEMORRHOIDS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
DIARRHOEA			
subjects affected / exposed	5 / 6 (83.33%)	6 / 6 (100.00%)	2 / 6 (33.33%)
occurrences (all)	10	9	2
PROCTITIS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
NAUSEA			
subjects affected / exposed	6 / 6 (100.00%)	4 / 6 (66.67%)	1 / 6 (16.67%)
occurrences (all)	7	4	1
ABDOMINAL PAIN			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
ORAL DISCOMFORT			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
DYSPEPSIA			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
ECCHYMOSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPERHIDROSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
RASH			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	3 / 6 (50.00%)
occurrences (all)	2	2	4
SKIN ULCER			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0

DERMATITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PRURITUS			
subjects affected / exposed	2 / 6 (33.33%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	3
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
ERYTHEMA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
DRY SKIN			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
SEBORRHOEA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
ALOPECIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
URINARY TRACT PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
URINARY INCONTINENCE			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
POLLAKIURIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
RENAL COLIC			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
RENAL FAILURE			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
HYPERPARATHYROIDISM			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPOTHYROIDISM			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPERTHYROIDISM			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
MUSCLE SPASMS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
BACK PAIN			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
OSTEOARTHRITIS			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
BONE PAIN			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
ARTHRALGIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
PAIN IN EXTREMITY			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
BRONCHIOLITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
INFLUENZA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
EAR INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
ORAL HERPES			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
IMPETIGO			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
OTITIS EXTERNA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
SINUSITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
RESPIRATORY SYNCYTIAL VIRUS INFECTION			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
RASH PUSTULAR			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
HERPES SIMPLEX			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HERPES ZOSTER			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
NASOPHARYNGITIS			
subjects affected / exposed	1 / 6 (16.67%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
CONJUNCTIVITIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	2
SKIN INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PNEUMONIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
CELLULITIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
SALMONELLOSIS			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
WOUND INFECTION			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
CANDIDA INFECTION			
subjects affected / exposed	1 / 6 (16.67%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPONATRAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPERPHOSPHATAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPOKALAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
DECREASED APPETITE			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
HYPOMAGNESAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPOPHOSPHATAEMIA			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPOCALCAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPERKALAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
HYPERURICAEMIA			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
FOLATE DEFICIENCY			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	B: Cobimetinib + Venetoclax	C: Cobimetinib + Venetoclax + Atezolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 16 (93.75%)	15 / 15 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
ADENOCARCINOMA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
ESSENTIAL HYPERTENSION			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
HAEMATOMA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
HYPERTENSION			

subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
PERIPHERAL VENOUS DISEASE			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
OEDEMA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
PYREXIA			
subjects affected / exposed	3 / 16 (18.75%)	3 / 15 (20.00%)	
occurrences (all)	3	4	
FEELING COLD			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
FACE OEDEMA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
PAIN			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
FATIGUE			
subjects affected / exposed	3 / 16 (18.75%)	3 / 15 (20.00%)	
occurrences (all)	5	3	
ASTHENIA			
subjects affected / exposed	2 / 16 (12.50%)	2 / 15 (13.33%)	
occurrences (all)	4	2	
CHEST PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
OEDEMA PERIPHERAL			

subjects affected / exposed	2 / 16 (12.50%)	2 / 15 (13.33%)	
occurrences (all)	4	2	
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
BALANOPOSTHITIS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
DYSPNOEA			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
EPISTAXIS			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
SINUS PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
COUGH			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Investigations			
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
NEUTROPHIL COUNT DECREASED			

subjects affected / exposed	3 / 16 (18.75%)	2 / 15 (13.33%)	
occurrences (all)	5	3	
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
BLOOD POTASSIUM DECREASED			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
VITAMIN B12 DECREASED			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
INFLUENZA A VIRUS TEST POSITIVE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	4 / 16 (25.00%)	2 / 15 (13.33%)	
occurrences (all)	4	6	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	4	
EJECTION FRACTION DECREASED			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
WEIGHT DECREASED			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
TROPONIN T INCREASED			

subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)		
occurrences (all)	0	3		
PLATELET COUNT DECREASED				
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)		
occurrences (all)	2	2		
LYMPHOCYTE COUNT DECREASED				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
BLOOD CREATINE INCREASED				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
HAEMOGLOBIN DECREASED				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
TROPONIN INCREASED				
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
LIPASE INCREASED				
subjects affected / exposed	1 / 16 (6.25%)	3 / 15 (20.00%)		
occurrences (all)	7	5		
BLOOD ALKALINE PHOSPHATASE INCREASED				
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)		
occurrences (all)	2	1		
BLOOD URIC ACID INCREASED				
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
AMYLASE INCREASED				
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)		
occurrences (all)	1	4		
WHITE BLOOD CELL COUNT DECREASED				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
BLOOD CALCIUM INCREASED				

subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
EYE CONTUSION			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
FALL			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
ATRIOVENTRICULAR BLOCK			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
CARDIAC FAILURE			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
NEURALGIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
SYNCOPE			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	3	
DYSGEUSIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
PARAESTHESIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
SCIATICA			

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
HYPERSOMNIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
DYSAESTHESIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
AUTONOMIC NEUROPATHY			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
POST HERPETIC NEURALGIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
HYPERAESTHESIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
HYPOAESTHESIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
LYMPHOPENIA			
subjects affected / exposed	1 / 16 (6.25%)	4 / 15 (26.67%)	
occurrences (all)	1	4	
NEUTROPENIA			
subjects affected / exposed	2 / 16 (12.50%)	7 / 15 (46.67%)	
occurrences (all)	2	17	
ANAEMIA			
subjects affected / exposed	9 / 16 (56.25%)	9 / 15 (60.00%)	
occurrences (all)	11	14	

FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 16 (18.75%)	5 / 15 (33.33%)	
occurrences (all)	3	5	
PANCYTOPENIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
LEUKOPENIA			
subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	9	
HAEMORRHAGIC DIATHESIS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
VERTIGO			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
EYE HAEMORRHAGE			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
DETACHMENT OF RETINAL PIGMENT EPITHELIUM			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
RETINAL HAEMORRHAGE			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
OPTIC NERVE CUPPING			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
DRY EYE			

subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
VISUAL IMPAIRMENT			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
PHOTOPHOBIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
SWELLING OF EYELID			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
SUBRETINAL FLUID			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
BLEPHAROCHALASIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
CHALAZION			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
BLEPHARITIS			
subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
DYSPHAGIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
MELAENA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
CONSTIPATION			

subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
VOMITING			
subjects affected / exposed	6 / 16 (37.50%)	3 / 15 (20.00%)	
occurrences (all)	10	8	
FLATULENCE			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
ORAL PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
DRY MOUTH			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
FAECES DISCOLOURED			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
HAEMATEMESIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
STOMATITIS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
GASTROINTESTINAL PAIN			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
ANORECTAL DISCOMFORT			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
HAEMORRHOIDS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
DIARRHOEA			

subjects affected / exposed	13 / 16 (81.25%)	13 / 15 (86.67%)	
occurrences (all)	17	21	
PROCTITIS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
NAUSEA			
subjects affected / exposed	5 / 16 (31.25%)	10 / 15 (66.67%)	
occurrences (all)	7	11	
ABDOMINAL PAIN			
subjects affected / exposed	0 / 16 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
ORAL DISCOMFORT			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
DYSPEPSIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ECCHYMOSIS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
HYPERHIDROSIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
RASH			
subjects affected / exposed	1 / 16 (6.25%)	5 / 15 (33.33%)	
occurrences (all)	1	6	
SKIN ULCER			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
DERMATITIS			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
PRURITUS			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
ERYTHEMA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
DRY SKIN			
subjects affected / exposed	1 / 16 (6.25%)	5 / 15 (33.33%)	
occurrences (all)	1	5	
SEBORRHOEA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
DERMATITIS ACNEIFORM			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
ALOPECIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
URINARY TRACT PAIN			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
URINARY INCONTINENCE			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
POLLAKIURIA			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
RENAL COLIC			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
RENAL FAILURE			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			

HYPERPARATHYROIDISM			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
HYPOTHYROIDISM			
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
HYPERTHYROIDISM			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
MUSCLE SPASMS			
subjects affected / exposed	3 / 16 (18.75%)	0 / 15 (0.00%)	
occurrences (all)	5	0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
BACK PAIN			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
OSTEOARTHRITIS			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
BONE PAIN			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
ARTHRALGIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	2 / 16 (12.50%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
BRONCHIOLITIS			

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
INFLUENZA				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
EAR INFECTION				
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
ORAL HERPES				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
IMPETIGO				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	4	0		
INFECTION				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
OTITIS EXTERNA				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
URINARY TRACT INFECTION				
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)		
occurrences (all)	2	1		
SINUSITIS				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
RESPIRATORY SYNCYTIAL VIRUS INFECTION				
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
RASH PUSTULAR				
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
HERPES SIMPLEX				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		

HERPES ZOSTER				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
NASOPHARYNGITIS				
subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)		
occurrences (all)	0	5		
CONJUNCTIVITIS				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)		
occurrences (all)	2	2		
SKIN INFECTION				
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)		
occurrences (all)	1	0		
PNEUMONIA				
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)		
occurrences (all)	2	1		
DEVICE RELATED INFECTION				
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
ORAL CANDIDIASIS				
subjects affected / exposed	1 / 16 (6.25%)	1 / 15 (6.67%)		
occurrences (all)	1	4		
RESPIRATORY TRACT INFECTION				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
PNEUMONIA PNEUMOCOCCAL				
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)		
occurrences (all)	0	0		
CELLULITIS				
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)		
occurrences (all)	0	1		
SALMONELLOSIS				

subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
WOUND INFECTION			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
CANDIDA INFECTION			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
HYPERTRIGLYCERIDAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
HYPONATRAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
HYPERPHOSPHATAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
HYPOKALAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	2	
DECREASED APPETITE			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
HYPOMAGNESAEMIA			
subjects affected / exposed	2 / 16 (12.50%)	1 / 15 (6.67%)	
occurrences (all)	5	2	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	3 / 15 (20.00%)	
occurrences (all)	0	6	
HYPOCALCAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
HYPERKALAEMIA			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

HYPERURICAEMIA			
subjects affected / exposed	1 / 16 (6.25%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
FOLATE DEFICIENCY			
subjects affected / exposed	0 / 16 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2017	The following updates were made: 1) Safety data for cobimetinib plus venetoclax was updated; 2) Information was added regarding the Cobimetinib plus Venetoclax plus Atezolizumab Safety Run-In Cohort design; 3) Clarifications were made to the Definition of Evaluable Patients in the Safety Run-In Cohorts and the Determination of Sample Size; 4) Pregnancy testing was updated; 5) Instructions for recordings of participant vital signs and left ventricular dysfunction were updated.
02 March 2018	The following updates were made: 1) Clinical data for atezolizumab was updated; 2) Updated the potential risk associated with atezolizumab; 3) Guidelines for atezolizumab-related dose modification and treatment interruption or discontinuation were updated; 4) Guidelines for managing patients who experience atezolizumab-associated AEs was updated; 5) Appendix 8 was added to the protocol.
20 September 2018	The following updates were made: 1) The number of participants randomized to each treatment arm was modified; 2) Inclusion criteria was updated; 3) Prohibited therapies were updated; 4) The timing of the optional bone marrow biopsy was changed; 5) Instructions on participant withdrawl were modified; 6) Lists of risks for atezolizumab were revised; 7) The maximum time for interrupting atezolizumab treatment was changed; 8) AESIs were revised; 9) Clarification of reporting of events that occur after study drug initiation.
27 March 2019	The following updates were made: 1) Enrollment of new participants was put on hold and a decision to continue study treatment for participants already enrolled would be made on a case-by-case basis; 2) The protocol was updated with topline data from an ongoing study; 3) Language was added to clarify recommendations on the administration of certain vaccinations; 4) The list of permitted therapies was updated; 5) Guidelines for managing hematological toxicities was modified; 6) A section was added to the protocol to address the management of infective complications.
24 January 2020	The following updates were made: 1) Background information on atezolizumab was updated; 2) "Immune-related" was changed to "immune-mediated" when describing events associated with atezolizumab; 3) Clinical data for cobimetinib plus venetoclax was updated; 4) Language clarified that after withdrawal of consent for participation in the Research Biosample Repository (RBR), remaining samples would be destroyed or no longer linked to the participant; 5) Identified risks associated with cobimetinib were updated; 6) Cobimetinib safety risk data was updated; 7) Serious infection, an important risk for venetoclax was closely monitored across all indications; 8) The list of atezolizumab risks was updated; 9) Systemic immune activation was replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab. The management guidelines for systemic immune activation were replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome; 10) AESIs were updated; 11) Language was revised as some site might not allow follow-up on partner pregnancies; 11) Language was updated that therapeutic or elective abortions were not considered AEs; 12) The atezolizumab AE management guidelines were revised.

18 February 2021	The following updates were made: 1) The list of approved indications for atezolizumab was updated; 2) Clarification for the use of investigational medicinal product accountability; 3) Immunosuppressive medications were removed from the prohibited therapy and added to the cautionary therapy for atezolizumab-treated participants; 4) Updates to the identified risks associated with cobimetinib; 5) The list of identified risks for atezolizumab was revised; 6) Guidelines for the management of atezolizumab-associated AEs and IRRs were revised; 7) The list of atezolizumab-associated AESIs was revised; 8) Language was added regarding female participants informing the investigator if they became pregnant; 9) Appendix 7 of the protocol was revised; 10) AE management guidelines for IRRs and CRS' were updated; 11) The management guidelines for HLH and MAS have been modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

In March 2019, this study was placed on voluntary enrollment hold. In May 2019, after an informal efficacy review, the Sponsor decided not to remove the hold and discontinued further development of the combination.

Notes: