Clinical trial results:
A phase II, multicenter, open-label, randomized-controlled trial evaluating the efficacy and safety of a sequencing schedule of cobimetinib plus vemurafenib followed by immunotherapy with an anti-PD-L1 antibody atezolizumab for the treatment in patients with unresectable or metastatic BRAF V600 mutant melanoma

Summary

EudraCT number	2015-005097-37
Trial protocol	DE FR GR
Global end of trial date	18 March 2024
Results information	
Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025
Summary attachment (see zip file)	ImmunoCobiVem_Synopsis_Final_v1.0_2025-03-18_all_redacted (ImmunoCobiVem_CSR+summary_final_v1.0_2025-03-

Trial information

Trial identification	
Sponsor protocol code	ImmunoCobiVem_2015
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02902029
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	University Hospital Essen
Sponsor organisation address	Hufelandstraße 55, Essen, Germany, 45122
Public contact	Departement of Dermatology, University Hospital Essen, 0049 2017234342, dirk.schadendorf@uk-essen.de
Scientific contact	Departement of Dermatology, University Hospital Essen, 0049 2017234342, dirk.schadendorf@uk-essen.de

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	09 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to assess if an early switch (i.e. switch at 3 months) from targeting the Ras/Raf signalling pathway by BRAF and MEK inhibition to immunologic checkpoint inhibition with an anti-PD-L1 antibody leads to prolongation of progressionfree and overall survival outcomes in patients with unresectable or metastatic BRAFV600 mutant melanoma. Furthermore, the safety of the study treatment will be assessed. The following endpoints will help to address the study objectives:
Primary endpoint:
PFS1 defined as time from start of run-in phase (date of first intake of study drug) to first documented tumor progression date according to RECIST v. 1.1 (PD1) or death by any cause, whichever occurs first (Figure 2). PFS1 will be based on the disease assessment or date of death provided by the local investigator. For patients who remain alive and whose disease has not progressed, PFS1 will be censored on the date of last visit/contact when a disease assessment was performed.

Protection of trial subjects:

The treatment was conducted as described in the protocol. The regulatory basis of the conduct of this study consisted of the Declaration of Helsinki (in its current version), the AMG [German Medicinal Products Act] / Regulation EU No 536/2014 (Clinical Trials Regulation), Regulation (EU) 2016/679 (General Data Protection Regulation), and the principles of the proper conduct of clinical trials (ICH GCP).
Any protocol deviations were reported. Throughout the study, participants were under close observation.

Background therapy:

All treatments that the investigator considered necessary for a subject’s welfare and that did not interfere with the trial drugs could be administered at the discretion of the investigator in keeping with the community standards of medical care.

Evidence for comparator:

After the 3 month run-in phase during which patients received vemurafenib and cobimetinib, patients who did not show disease progression or treatment interruption for more than 28 days during run-in phase were randomized in a 1:1 ratio either to proceed vemurafenib and cobimetinib until disease progression and subsequently cross over to atezolizumab treatment until disease progression (Arm A) or to receive atezolizumab treatment until disease progression and subsequently cross back to vemurafenib and cobimetinib until disease progression (Arm B).

Actual start date of recruitment	23 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 117
Country: Number of subjects enrolled	Greece: 30
Country: Number of subjects enrolled	Serbia: 21

Worldwide total number of subjects	185
EEA total number of subjects	164

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)	112
From 65 to 84 years	67
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Patients were selected by the investigator. After obtaining signed informed consent, patients were screened to ensure that they meet the inclusion and exclusion criteria. Between November 23, 2016 and December 27, 2019, 244 patients were assessed for eligibility, including 59 screening failures. Thus, 185 patients could be enrolled.

Pre-assignment

Screening details:

Patients withBRAF V600 melanoma stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c that fullfilled the inclusion / excluison criteria were included in the run-in-phase and were treated with a combination of vemurafenib and cobimetinib. Screening evaluations had to be performed within 28 days before administration of first study treatment.

Period 1

Period 1 title	Run-in period
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No blinding; Study treatmetn was administered in an open-label manner.

Arms

Arm title	Run-in

Arm description:

All enrolled patients were treated with vemurafenib and cobimetinib. Vemurafenib and cobimetinib were administered in 28-days cycles. During the run-in phase, vemurafenib and cobimetinib were given for three cycles.

Arm type	Run-in Phase
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	Zelboraf
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose of vemurafenib was 960 mg (4 tablets of 240 mg) taken orally twice daily (equivalent to a total daily dose of 1,920 mg). The first dose of vemurafenib was taken in the morning, and the second dose was taken in the evening, at least 8 hours after the first dose (the ideal interval between the doses was 12 hours). Vemurafenib was taken continuously during each 28-day cycle.

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 taken orally in a 28-day cycle. Each dose consisted of three 20 mg tablets (60 mg in total). Cobimetinib was taken once daily for 21 consecutive days (days 1 to 21-treatment period), followed by a 7-day break (days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle was started after the 7-day treatment break was elapsed.
Cobimetinib was taken once daily at approximately the same time each day with the morning vemurafenib dose, and not later than 4 hours after the scheduled time.

Number of subjects in period 1	Run-in
Started	185
Completed	135
Not completed	50
Physician decision	2
Consent withdrawn by subject	2
Adverse event, non-fatal	28
Patient's wish	4
Death	3
Progression of primary disease	11

Period 2

Period 2 title	Randomized phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

No blinding; study medication was administered open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (CobiVem, switch to Atezolizumab)

Arm description:

Patients who terminated the three cycles of the Run-in phase without progressive disease were randomized. Patients randomized to Arm A proceeded vemurafenib and cobimetinib. If a patient required a dose reduction of vemurafenib and / or cobimetinib during the Run-in phase due to toxicity, vemurafenib and cobimetinib were administered for this patient with the reduced dose during the randomized phase. Treatment was continued until unacceptable toxicities, patient's wish, withdrawal of informed consent, investigator's decision or progression ot the disease. Patients wiht disease progression (except of brain metastases) were subsequently crossed-over to atezolizumab treatment (1,200 mg / q3w).

Arm type	Active comparator
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	Zelboraf
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The starting dose of vemurafenib was 960 mg (4 tablets of 240 mg) taken orally twice daily (equivalent to a total daily dose of 1,920 mg). The first dose of vemurafenib was taken in the morning, and the second dose was taken in the evening, at least 8 hours after the first dose (the ideal interval between the doses was 12 hours). Vemurafenib was taken continuously during each 28-day cycle.

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 taken orally in a 28-day cycle. Each dose consisted of three 20 mg tablets (60 mg in total). Cobimetinib was taken once daily for 21 consecutive days (days 1 to 21-treatment period), followed by a 7-day break (days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle was started after the 7-day treatment break was elapsed.
Cobimetinib was taken once daily at approximately the same time each day with the morning vemurafenib dose, and not later than 4 hours after the scheduled time.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose level of atezolizumab tested in this study was 1,200 mg (equivalent to an average body weight based dose of 15 mg/kg) administered by IV infusion q3w (21 [± 3] days) according to the FDA-approved prescribing information for atezolizumab. The initial dose of atezolizumab was delivered over 60 (± 15) minutes. If the first infusion was tolerated without infusion-associated adverse events and cytokine release syndrome, the second infusion was delivered over 30 (± 10) minutes. If the 30-minute infusion was well tolerated, all subsequent infusions were delivered over 30 (± 10) minutes. At all infusions, the patient’s vital signs (heart rate, respiratory rate, blood pressures, and temperature) were determined within 60 minutes before and 30 (± 10) minutes after the infusion. Vital signs were also collected during the first infusion (every 15 [± 5] minutes). During subsequent infusions, vital signs were collected if clinically indicated.

Arm title	Arm B (Atezolizumab, switch to CobiVem)

Arm description:

Patients who terminated the three cycles of the Run-in phase without progressive disease were randomized. Patients who were randomized to Arm B received 1,200 mg atezolizumab administered by IV infusion q3w (21 [± 3] days). Treatment was continued until unacceptable toxicities, patient's wish, withdrawal of informed consent, investigator's decision or progression of the disease. Patients with disease progression (except of brain metastases) were subsequently crossed over to treatment with vemurafenib (960 mg) and cobimetinib (60 mg QD).

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	Tecentriq
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose level of atezolizumab tested in this study was 1,200 mg (equivalent to an average body weight based dose of 15 mg/kg) administered by IV infusion q3w (21 [± 3] days) according to the FDA-approved prescribing information for atezolizumab. The initial dose of atezolizumab was delivered over 60 (± 15) minutes. If the first infusion was tolerated without infusion-associated adverse events and cytokine release syndrome, the second infusion was delivered over 30 (± 10) minutes. If the 30-minute infusion was well tolerated, all subsequent infusions were delivered over 30 (± 10) minutes. At all infusions, the patient’s vital signs (heart rate, respiratory rate, blood pressures, and temperature) were determined within 60 minutes before and 30 (± 10) minutes after the infusion. Vital signs were also collected during the first infusion (every 15 [± 5] minutes). During subsequent infusions, vital signs were collected if clinically indicated.

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

Dosage and administration details:

The starting dose of vemurafenib was 960 mg (4 tablets of 240 mg) taken orally twice daily (equivalent to a total daily dose of 1,920 mg). The first dose of vemurafenib was taken in the morning, and the second dose was taken in the evening, at least 8 hours after the first dose (the ideal interval between the doses was 12 hours). Vemurafenib was taken continuously during each 28-day cycle.

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 taken orally in a 28-day cycle. Each dose consisted of three 20 mg tablets (60 mg in total). Cobimetinib was taken once daily for 21 consecutive days (days 1 to 21-treatment period), followed by a 7-day break (days 22 to 28-treatment break). Each subsequent cobimetinib treatment cycle was started after the 7-day treatment break was elapsed.
Cobimetinib was taken once daily at approximately the same time each day with the morning vemurafenib dose, and not later than 4 hours after the scheduled time.

Number of subjects in period 2	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)
Started	69	66
Switch to treatment of other arm	21	35
Completed	7	6
Not completed	62	60
Physician decision	3	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	12	4
Patient's wish	7	3
Death	3	4
Other reason	3	10
Progression of primary disease	27	29
Brain metastasis	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Run-in period

Reporting group description: -

Reporting group values	Run-in period	Total	
Number of subjects	185	185	
Age categorical			
Age per patient was calculated as 'age at enrollment' minus 'date of birth'.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	112	112	
From 65-84 years	67	67	
85 years and over	6	6	
Age continuous			
Age per patient was calculated as 'age at date of enrollment' minus 'date of birth'.			
Units: years			
median	58		
full range (min-max)	19 to 91	-	
Gender categorical			
Men and women could be enrolled, as no sex specific differences were expected concerning the efficacy and safety of the used trial medication.			
Units: Subjects			
Female	68	68	
Male	117	117	

End points

End points reporting groups

Reporting group title	Run-in

Reporting group description:

All enrolled patients were treated with vemurafenib and cobimetinib. Vemurafenib and cobimetinib were administered in 28-days cycles. During the run-in phase, vemurafenib and cobimetinib were given for three cycles.

Reporting group title	Arm A (CobiVem, switch to Atezolizumab)

Reporting group description:

Patients who terminated the three cycles of the Run-in phase without progressive disease were randomized. Patients randomized to Arm A proceeded vemurafenib and cobimetinib. If a patient required a dose reduction of vemurafenib and / or cobimetinib during the Run-in phase due to toxicity, vemurafenib and cobimetinib were administered for this patient with the reduced dose during the randomized phase. Treatment was continued until unacceptable toxicities, patient's wish, withdrawal of informed consent, investigator's decision or progression ot the disease. Patients wiht disease progression (except of brain metastases) were subsequently crossed-over to atezolizumab treatment (1,200 mg / q3w).

Reporting group title	Arm B (Atezolizumab, switch to CobiVem)

Reporting group description:

Patients who terminated the three cycles of the Run-in phase without progressive disease were randomized. Patients who were randomized to Arm B received 1,200 mg atezolizumab administered by IV infusion q3w (21 [± 3] days). Treatment was continued until unacceptable toxicities, patient's wish, withdrawal of informed consent, investigator's decision or progression of the disease. Patients with disease progression (except of brain metastases) were subsequently crossed over to treatment with vemurafenib (960 mg) and cobimetinib (60 mg QD).

Primary: Progression-free survival 1 (PFS1)

End point title	Progression-free survival 1 (PFS1)

End point description:

PFS 1 was defined as time from start of run-in phase (date of first intake of study drug) to first documented tumor progression date according to RECIST v. 1.1 (PD1) or death by any cause, whichever occurred first. PFS1 was based on the disease assessment or date of death provided by the local investigator. For patients who remained alive and whose disease had not progressed, PFS1 was censored on the date of last visit/contact when a disease assessment was performed
The analysis of the primary endpoint was based on the 'primary endpoint population' (PEP), which included all randomized patients who had at least one dose of the scheduled treatment in the randomized phase and who did not have had major disqualifying protocol violations. One patient in each arm was excluded from the PEP due to protocol violation (= Patients were randomized despite having a progress during the Run-in phase).

End point type	Primary

End point timeframe:

Time from start of run-in phase (date of first intake of study drug) to first documented tumor progression date according to RECIST v. 1.1 (= PD1) or death by any cause, whichever occurred first.

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	65		
Units: months				
median (confidence interval 95%)	12.96 (9.87 to	5.94 (5.46 to		

15.59)	8.29)

Statistical analyses

Statistical analysis title	PFS1_primary endpoint population

Statistical analysis description:

Comparison of the progression-free survival of the 2 randomized arms.

Comparison groups	Arm B (Atezolizumab, switch to CobiVem) v Arm A (CobiVem, switch to Atezolizumab)
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0141
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.91

Secondary: Progression-free survival 2 (PFS2)

End point title	Progression-free survival 2 (PFS2)

End point description:

PFS2 was defined as time from start of run-in phase (date of first intake of study drug) to second documented disease progression according to RECIST v. 1.1 (PD2, progression after therapy switch) following randomization or death by any cause. PFS2 was based on the disease assessment or date of death provided by the local investigator. For patients who remained alive and whose disease had not progressed, PFS2 was censored on the date of last visit/contact when a disease assessment was performed. Analysis was based on the randomized patients, who switched therapy after the 1st progression.

End point type	Secondary

End point timeframe:

Time from start of run-in phase (date of first intake of study drug) to second objective disease progression according to RECIST v. 1.1 (PD2) following randomization or death by any cause.

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[1]	35[2]		
Units: month				

median (confidence interval 95%)	12.57 (8.32 to 17.01)	14.61 (8.55 to 25.56)		

Notes:

[1] - Patients in Arm A with switch

[2] - Patients in Arm B with switch

Statistical analyses

Statistical analysis title	PFS2_switch patients
Comparison groups	Arm A (CobiVem, switch to Atezolizumab) v Arm B (Atezolizumab, switch to CobiVem)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4069
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.38

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall Survival (OS) of patients was defined as the time from start of run-in phase (date of first intake of study drug) until documented date of death, for any cause. Patients still alive were censored at the time of last visit/contact. Analysis was based on the randomized patients of the run-in phase (Intention-to Treat population (ITT)).

End point type	Secondary

End point timeframe:

Time from start of run-in phase (date of first intake of study drug) until documented date of death, for any cause.

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: months				
median (confidence interval 95%)	40.23 (18.88 to 1000)	49.64 (26.05 to 1000)		

Statistical analyses

Statistical analysis title	OS_ITT
Comparison groups	Arm A (CobiVem, switch to Atezolizumab) v Arm B (Atezolizumab, switch to CobiVem)
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5339
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.91

Secondary: Overall survival rate at 12 months

End point title	Overall survival rate at 12 months

End point description:

Overall survival rate at 12 months was defined as the rate of patients alive 12 months after start of run-in phase (date of first intake of study drug). Analysis was based on the Intention-to-Treat population (ITT).

End point type	Secondary

End point timeframe:

12 months after start of run-in phase (date of first intake of study drug).

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: patients	55	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 24 months

End point title	Overall survival rate at 24 months

End point description:

Overall survival rate at 24 months was defined as the rate of patients alive 24 months after start of run-in phase (date of first intake of study drug). Analysis was based on the Intention-to-Treat population (ITT).

End point type	Secondary

End point timeframe:

24 months after start of run-in phase (date of first intake of study drug).

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: patients	43	47		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 36 months

End point title	Overall survival rate at 36 months

End point description:

Overall survival rate at 36 months was defined as the rate of patients alive 36 months after start of run-in phase (date of first intake of study drug). Analysis was based on the Intention-to-Treat population (ITT).

End point type	Secondary

End point timeframe:

36 months after start of run-in phase (date of first intake of study drug).

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: patients	41	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 48 months

End point title	Overall survival rate at 48 months

End point description:

Overall survival rate at 24 months was defined as the rate of patients alive 24 months after start of run-in phase (date of first intake of study drug). Analysis was based on the Intention-to-Treat population (ITT).

End point type	Secondary

End point timeframe:

48 months after start of run-in phase (date of first intake of study drug).

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: patients	35	40		

Statistical analyses

No statistical analyses for this end point

Secondary: 12-months DCR

End point title	12-months DCR

End point description:

Disease control rate (DCR) was defined as the rate of patients showing complete response (CR) or partial response (PR) or stable disease (SD) at 12 months after the start of run-in phase (date of first intake of study drug). Analysis was based on the Intention-to Treat population (ITT).

End point type	Secondary

End point timeframe:

12 months after the start of run-in phase (date of first intake of study drug).

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: patients	31	16		

Statistical analyses

No statistical analyses for this end point

Secondary: 24-months DCR

End point title	24-months DCR

End point description:

DCR was defined as the rate of patients showing complete response (CR) or partial response (PR) or stable disease (SD) at 12 months after the start of run-in phase (date of first intake of study drug).

Analysis was based on the Intention-to Treat population (ITT).

End point type	Secondary

End point timeframe:

24 months after the start of run-in phase (date of first intake of study drug).

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: patients	13	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall objective response rate (OORR)

End point title	Best overall objective response rate (OORR)

End point description:

OORR was defined as the rate of patients showing complete response (CR) or partial response (PR) according to RECIST v1.1 Criteria. Analysis was based on the Intention-to Treat population (ITT).

End point type	Secondary

End point timeframe:

From the start of run-in phase (date of first intake of study drug) until the end of the study.

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	66		
Units: patients	56	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of patients with PD and without change to subsequent therapy line

End point title	Rate of patients with PD and without change to subsequent therapy line

End point description:

Rate of patients with progressive disease (PD) who could not change to subsequent line of therapy due to deterioration of ECOG status or multiple and/or symptomatic brain metastasis and/or leptomeningeal

disease
o from vemurafenib + cobimetinib to atezolizumab (Arm A)
o from atezolizumab to vemurafenib + cobimetinib (Arm B)
Analysis was based on the Intention-to Treat population (ITT).

End point type	Secondary

End point timeframe:

From the start of run-in phase (date of first intake of study drug) until first documented PD (PD1) after randomization.

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37[3]	50[4]		
Units: patients	16	15		

Notes:

[3] - Patients with progressive disease during treatment with vemurafenib and cobimetinib

[4] - Patients with progressive disease during atezolizumab treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival 3 (PFS3)

End point title	Progression-free survival 3 (PFS3)

End point description:

PFS3 was based on the disease assessment or date of death provided by the local investigator. For patients who remained alive and whose disease had not progressed, PFS3 was censored on the date of last visit/contact when a disease assessment was performed. Analysis was based on the patients of the Intention-to Treat population (ITT), who switched therapy after the 1st progression.

End point type	Secondary

End point timeframe:

Time from the first documented tumor progression date (PD1) after randomization until the second documented tumor progression date (PD2) or death by any cause, whichever occurred first.

End point values	Arm A (CobiVem, switch to Atezolizumab)	Arm B (Atezolizumab, switch to CobiVem)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[5]	35[6]		
Units: months				
median (confidence interval 95%)	2.83 (2.14 to 3.32)	6.02 (2.14 to 8.75)		

Notes:

[5] - Patients in Arm A with switch

[6] - Patients in Arm B with switch

Statistical analyses

Statistical analysis title	PFS3_switch patients
Comparison groups	Arm A (CobiVem, switch to Atezolizumab) v Arm B (Atezolizumab, switch to CobiVem)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0801
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	3.2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of written consent until 90 days of discontinuation of dosing of the investigational product.

Adverse event reporting additional description:

All patients who received at least one dose of study treatment with vemurafenib and cobimetinib during the run-in phase of the study were considered evaluable for safety parameters. Safety was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4.03

Reporting groups

Reporting group title	Safety Population

Reporting group description:

The safety population (SP) comprised a total of 182 enrolled patients, who received at least one dose of the investigational agent(s).

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 182 (52.75%)		
number of deaths (all causes)	88		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pituitary tumour benign			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 182 (1.65%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	4 / 182 (2.20%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Malaise			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	4 / 182 (2.20%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 182 (1.65%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			

subjects affected / exposed	3 / 182 (1.65%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ejection fraction decreased			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Troponin T increased			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain radiation necrosis			

subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	3 / 182 (1.65%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint injury				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medication error				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Product administration error				

subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Splinter				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Aortic valve disease				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiopulmonary failure				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dysfunction				

subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Demyelination			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	3 / 182 (1.65%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 2		
Monoparesis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia				
subjects affected / exposed	5 / 182 (2.75%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Eosinophilia				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemolytic anaemia				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Diplopia				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pterygium				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	3 / 182 (1.65%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	7 / 182 (3.85%)			
occurrences causally related to treatment / all	7 / 7			
deaths causally related to treatment / all	0 / 0			

Gastritis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 182 (1.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal haemorrhage				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal haemorrhage				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 182 (1.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Bile duct stenosis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder obstruction				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated hepatitis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermo-hypodermitis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis exfoliative generalised				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug reaction with eosinophilia and				

systemic symptoms				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema multiforme				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash maculo-papular				
subjects affected / exposed	8 / 182 (4.40%)			
occurrences causally related to treatment / all	8 / 9			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson syndrome				
subjects affected / exposed	2 / 182 (1.10%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	10 / 182 (5.49%)			
occurrences causally related to treatment / all	7 / 11			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Goitre				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Muscular weakness				

subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoporosis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cholecystitis infective				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				

subjects affected / exposed	3 / 182 (1.65%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung abscess				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 182 (2.75%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 182 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	7 / 182 (3.85%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	2 / 182 (1.10%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				

subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	181 / 182 (99.45%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 182 (14.29%)		
occurrences (all)	33		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	19 / 182 (10.44%)		
occurrences (all)	22		
Fatigue			

subjects affected / exposed	71 / 182 (39.01%)		
occurrences (all)	103		
Influenza like illness			
subjects affected / exposed	22 / 182 (12.09%)		
occurrences (all)	30		
Oedema peripheral			
subjects affected / exposed	15 / 182 (8.24%)		
occurrences (all)	18		
Pain			
subjects affected / exposed	15 / 182 (8.24%)		
occurrences (all)	18		
Pyrexia			
subjects affected / exposed	56 / 182 (30.77%)		
occurrences (all)	93		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 182 (6.59%)		
occurrences (all)	12		
Dyspnoea			
subjects affected / exposed	20 / 182 (10.99%)		
occurrences (all)	23		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 182 (5.49%)		
occurrences (all)	13		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	45 / 182 (24.73%)		
occurrences (all)	65		
Amylase increased			
subjects affected / exposed	20 / 182 (10.99%)		
occurrences (all)	25		
Aspartate aminotransferase increased			
subjects affected / exposed	43 / 182 (23.63%)		
occurrences (all)	60		
Blood alkaline phosphatase increased			

subjects affected / exposed	33 / 182 (18.13%)		
occurrences (all)	54		
Blood bilirubin increased			
subjects affected / exposed	19 / 182 (10.44%)		
occurrences (all)	33		
Blood creatine phosphokinase increased			
subjects affected / exposed	51 / 182 (28.02%)		
occurrences (all)	104		
Blood creatinine increased			
subjects affected / exposed	42 / 182 (23.08%)		
occurrences (all)	58		
Gamma-glutamyltransferase increased			
subjects affected / exposed	44 / 182 (24.18%)		
occurrences (all)	68		
Lipase increased			
subjects affected / exposed	40 / 182 (21.98%)		
occurrences (all)	83		
Lymphocyte count decreased			
subjects affected / exposed	27 / 182 (14.84%)		
occurrences (all)	59		
Electrocardiogram QT prolonged			
subjects affected / exposed	15 / 182 (8.24%)		
occurrences (all)	17		
Platelet count decreased			
subjects affected / exposed	12 / 182 (6.59%)		
occurrences (all)	18		
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	28 / 182 (15.38%)		
occurrences (all)	48		
Fall			
subjects affected / exposed	11 / 182 (6.04%)		
occurrences (all)	12		
Nervous system disorders			

Dysgeusia subjects affected / exposed occurrences (all)	11 / 182 (6.04%) 11		
Headache subjects affected / exposed occurrences (all)	21 / 182 (11.54%) 33		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	37 / 182 (20.33%) 55		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	13 / 182 (7.14%) 14		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	104 / 182 (57.14%) 360		
Nausea subjects affected / exposed occurrences (all)	51 / 182 (28.02%) 83		
Vomiting subjects affected / exposed occurrences (all)	38 / 182 (20.88%) 55		
Abdominal pain lower subjects affected / exposed occurrences (all)	16 / 182 (8.79%) 18		
Abdominal pain upper subjects affected / exposed occurrences (all)	10 / 182 (5.49%) 12		
Constipation subjects affected / exposed occurrences (all)	14 / 182 (7.69%) 15		
Dry mouth subjects affected / exposed occurrences (all)	11 / 182 (6.04%) 12		
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	18 / 182 (9.89%)		
occurrences (all)	18		
Dermatitis acneiform			
subjects affected / exposed	32 / 182 (17.58%)		
occurrences (all)	40		
Dry skin			
subjects affected / exposed	16 / 182 (8.79%)		
occurrences (all)	18		
Eczema			
subjects affected / exposed	10 / 182 (5.49%)		
occurrences (all)	11		
Erythema multiforme			
subjects affected / exposed	10 / 182 (5.49%)		
occurrences (all)	10		
Photosensitivity reaction			
subjects affected / exposed	57 / 182 (31.32%)		
occurrences (all)	84		
Pruritus			
subjects affected / exposed	23 / 182 (12.64%)		
occurrences (all)	29		
Rash			
subjects affected / exposed	11 / 182 (6.04%)		
occurrences (all)	19		
Rash maculo-papular			
subjects affected / exposed	69 / 182 (37.91%)		
occurrences (all)	93		
Solar dermatitis			
subjects affected / exposed	12 / 182 (6.59%)		
occurrences (all)	19		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	22 / 182 (12.09%)		
occurrences (all)	31		
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	31 / 182 (17.03%)		
occurrences (all)	34		
Hypothyroidism			
subjects affected / exposed	29 / 182 (15.93%)		
occurrences (all)	35		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	35 / 182 (19.23%)		
occurrences (all)	49		
Back pain			
subjects affected / exposed	14 / 182 (7.69%)		
occurrences (all)	18		
Myalgia			
subjects affected / exposed	15 / 182 (8.24%)		
occurrences (all)	20		
Pain in extremity			
subjects affected / exposed	31 / 182 (17.03%)		
occurrences (all)	36		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 182 (5.49%)		
occurrences (all)	11		
Conjunctivitis			
subjects affected / exposed	11 / 182 (6.04%)		
occurrences (all)	13		
Urinary tract infection			
subjects affected / exposed	11 / 182 (6.04%)		
occurrences (all)	16		
COVID-19			
subjects affected / exposed	12 / 182 (6.59%)		
occurrences (all)	17		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 182 (6.59%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2016	With Amendment No 1 (protocol version 1.3; dated July 12, 2016), questionnaires for patients regarding medication adherence and quality of life became part of the study. New exploratory objectives addressed by patient questionnaires were specified. Furthermore, the amendment included corrections and specification of wording throughout the protocol.
15 December 2016	Amendment No 2 (protocol version 1.4; dated December 15, 2016) included specification of inclusion and exclusion criteria and an update of risks associated with the study treatment. Moreover, the specification of the BRAF mutation was deleted. A reference for (S)AE documentation and new Adverse Events of Special Interest (AESI) were included and assessment schedules updated.
18 May 2017	With Amendment No 3 (protocol version 1.5; dated May 18, 2017) , changes regarding medication adherence questionnaires have been made.
12 December 2017	With Amendment No 4 (protocol version 1.6, dated December 12, 2017) timelines were updated, and clinical examination schedules were changed. Moreover, based on the updated atezolizumab Investigator Brochure (IB, version 10 from Jul 2017), changes regarding clinical experience and risks associated with atezolizumab were updated.
29 April 2019	Amendment No 5 (protocol version 1.8; dated April 29, 2019) included update of the study timelines, change of marketing authorization holder, adaptation of schedules of study visits and examinations. Furthermore, clinical experience and risks associated with atezolizumab were updated due to the release of revised IBs for cobimetinib (version 11, dated September 25, 2018), for vemurafenib (version 16, dated December 13, 2018) and for atezolizumab (version 14, dated October 24, 2018), and corresponding addendum 1 (dated December 05, 2018).
09 June 2020	With Amendment No 6 (protocol version 2.0; dated June 09, 2020) the primary endpoint was changed. The previous secondary endpoint progression-free survival (PFS) 1 is now analyzed as primary endpoint, and the previous primary endpoint PFS2 is now analyzed as secondary endpoint. During regular data review, it was noticed that there were patients not switching therapy after their first progress as planned according to protocol. These patients were previously not included in the primary endpoint population even though they received other therapies. In addition, the follow-up period was extended by two years, to collect further data for overall survival (OS). Moreover, an interim analysis was added in order to gain knowledge on the impact of an early switch from BRAF/MEK inhibition to PD-L1 inhibition on PFS1. This analysis was conducted after 80% of patients have reached PFS1 or prematurely discontinued the study. Furthermore, the protocol was updated according to the release of revised IBs for cobimetinib (version 12, dated September 2019 with new addendum), for vemurafenib (version 17, dated December 2019), and for atezolizumab (version 15, dated December 2019 with corresponding addendum 2). According to the sponsor, these revised documents did not affect the benefit-risk assessment for patients undergoing treatment within the study.
11 May 2021	Amendment No 7 (protocol version 3.0; dated May 11, 2021) included changes regarding safety and approved indications of atezolizumab based on the release of revised IBs for cobimetinib (version 13, dated September 2020), for vemurafenib (version 18, dated May 2020), and for atezolizumab (version 17, dated September 2020; version 16 was withdrawn from the marketing authorization holder and did not become effective). According to the sponsor, the revision of these documents did not affect the benefit-risk assessment for patients undergoing treatment within the study.

04 April 2022	Amendment No 8 (protocol version 4.0; dated April 26, 2022) included changes regarding new risks of vemurafenib and atezolizumab based on the release of revised IBs for vemurafenib (version 19, dated May 2021), and for atezolizumab (version 18 and Addendum 1, dated Jul and Aug 2021, respectively). Furthermore, changes in the management of atezolizumab-specific adverse events were issued. Updates on clinical trials were implemented in chapters 2.2, 2.3, 2.5 and 2.6. According to the sponsor, the revision of these documents did not affect the benefit-risk assessment for patients undergoing treatment within the study.
24 May 2023	Amendment No 9 (protocol version 5.0; dated 24 May 2023) included changes regarding safety and approved indications of cobimetinib and vemurafenib based on the release of revised IBs for vemurafenib (versions 20 and 21, dated May 2022 and May 2023, respectively), cobimetinib (version 15, Sep 2022) and for atezolizumab (version 19, dated Aug 2022). Risks associated with atezolizumab and cobimetinib as well as dose modifications and treatment alterations of study treatment were updated. Further, specification for cardiac evaluation was included in the 'schedule of visits and assessments'.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/40345056