Clinical trial results:
A phase II study investigating preoperative combination strategies for immunotherapy in patients with untreated, operable ER+, HER2-negative primary breast cancer.

Summary

EudraCT number	2016-004424-38
Trial protocol	GB DE
Global end of trial date	18 August 2023

Results information

Result version number	v1 (current)
This version publication date	04 September 2024
First version publication date	04 September 2024

Trial information

Trial identification

Sponsor protocol code	011604QM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03395899
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Mile End Road, London, United Kingdom, E1 2EF
Public contact	Charlotte Ackerman, Queen Mary University of London, +44 2078828197, bci-eclipse@qmul.ac.uk
Scientific contact	Charlotte Ackerman, Queen Mary University of London, +44 2078828197, bci-eclipse@qmul.ac.uk

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	17 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2023
Global end of trial reached?	Yes
Global end of trial date	18 August 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether adding immune-modulatory agents to atezolizumab increases the probability of an immune response over atezolizumab alone in patients with operable ER+ breast cancer.

Protection of trial subjects:

All enrolled patients will be evaluated clinically before and during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events and laboratory measurements. Eligibility criteria for this study were selected to enhance the safety of patients. A number of exclusion criteria are specifically based on the known safety profiles of the study treatment.

Background therapy:

Atezolizumab (also known as MPDL3280A or TECENTRIQ) is a human IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab targets PD-L1 on immune cells or tumour cells and prevents interaction with either PD-1 receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumour-specific T-cell response through increased T-cell priming, expansion, and/or effector function. At the time of study design, atezolizumab was approved in the United States for urothelial cancer.

Evidence for comparator:

PD1/PD-L1-targeting checkpoint inhibitors have shown limited single agent activity in ER+ breast cancer.

There is increasing evidence that CIT combinations can increase the activity of CIT by converting cancers into a more inflamed phenotype. This is particularly relevant for ER+ breast cancers which are predominantly non-inflamed.

A wide range of CIT combinations are undergoing investigation, but preclinical models are of limited use in prioritising treatments as they fail to represent the complex interactions between tumour and the immune system. Preoperative window trials provide a robust and efficient clinical model to rapidly evaluate and prioritise these novel CIT strategies.

Enrolment of multiple experimental arms within a single study, rather than one or two experimental arms within multiple studies, will result in an overall reduction in the number of patients receiving control arm treatment. More importantly, this study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumour infiltration, and/or recognition of tumour cells for elimination. To improve the confidence of clinical signal detection in the combination arms, this study will include a control arm in which patients will receive single agent atezolizumab.
Only combinations with adequate clinical safety data will be tested within this trial.

Actual start date of recruitment	01 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Korea, Republic of: 15
Worldwide total number of subjects	71
EEA total number of subjects	56

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)	71
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study opened to recruitment on 21Dec2017 and the first patient was consented on 30Jan2018. The study was halted to recruitment on 10 February 2022 due to low recruitment rate. However, enough data was collected in order to analyse the endpoints as planned.

Pre-assignment

Screening details:

78 patients were screened for the trial, with 71 patients randomised. 7 patients screen failed, 5 from Germany and 2 from UK.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Atezolizumab only

Arm description:

Control arm. Atezolizumab (1200 mg IV D1) .

Arm type	Active comparator
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg (equivalent to an average body weight-based dose of 15mg/kg) administered by IV infusion every 3 weeks (21 days). Atezolizumab was delivered over 60 (± 15) minutes.

Arm title	Atezolizumab + Cobimetinib

Arm description:

Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21)

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

Dosage and administration details:

1200 mg (equivalent to an average body weight-based dose of 15mg/kg) administered by IV infusion every 3 weeks (21 days). Atezolizumab was delivered over 60 (± 15) minutes.

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

Dosage and administration details:

Cobimetinib at a dose of 60 mg (three 20 mg tablets) orally once daily on Days 1−21.

Arm title	Atezolizumab + Ipatasertib

Arm description:

Atezolizumab (1200 mg IV D1)+ Ipatasertib (400 mg OD D1 – 21)

Arm type	Active comparator
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg (equivalent to an average body weight-based dose of 15mg/kg) administered by IV infusion every 3 weeks (21 days). Atezolizumab was delivered over 60 (± 15) minutes.

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

Dosage and administration details:

400 mg (two 200mg tablets) orally once a day on Days 1−21.

Arm title	Atezolizumab + Cobimetinib + Bevacizumab

Arm description:

Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21) + Bevacizumab (10 mg/kg IV D1)

Arm type	Active comparator
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg (equivalent to an average body weight-based dose of 15mg/kg) administered by IV infusion every 3 weeks (21 days). Atezolizumab was delivered over 60 (± 15) minutes.

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

Dosage and administration details:

Cobimetinib at a dose of 60 mg (three 20 mg tablets) orally once daily on Days 1−21.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg administered by IV infusion over 90 min on day 1 cycle 1

Number of subjects in period 1	Atezolizumab only	Atezolizumab + Cobimetinib	Atezolizumab + Ipatasertib
Started	27	9	27
Completed	27	9	27

Number of subjects in period 1	Atezolizumab + Cobimetinib + Bevacizumab
Started	8
Completed	8

Baseline characteristics

Reporting groups	
Reporting group title	Atezolizumab only
Reporting group description:	
Control arm. Atezolizumab (1200 mg IV D1) .	
Reporting group title	Atezolizumab + Cobimetinib
Reporting group description:	
Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21)	
Reporting group title	Atezolizumab + Ipatasertib
Reporting group description:	
Atezolizumab (1200 mg IV D1)+ Ipatasertib (400 mg OD D1 – 21)	
Reporting group title	Atezolizumab + Cobimetinib + Bevacizumab
Reporting group description:	
Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21) + Bevacizumab (10 mg/kg IV D1)	

Reporting group values	Atezolizumab only	Atezolizumab + Cobimetinib	Atezolizumab + Ipatasertib
Number of subjects	27	9	27
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)	27	9	27
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	27	9	27
Male	0	0	0

Reporting group values	Atezolizumab + Cobimetinib + Bevacizumab	Total	
Number of subjects	8	71	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	8	71	

From 65-84 years	0	0	
85 years and over	0	0	

Gender categorical Units: Subjects			
Female	8	71	
Male	0	0	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full analyis set of full trial population

Reporting group values	Full Analysis Set		
Number of subjects	71		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	71		
From 65-84 years	0		
85 years and over	0		
Gender categorical Units: Subjects			
Female	71		
Male	0		

End points

End points reporting groups

Reporting group title	Atezolizumab only
Reporting group description: Control arm. Atezolizumab (1200 mg IV D1) .	
Reporting group title	Atezolizumab + Cobimetinib
Reporting group description: Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21)	
Reporting group title	Atezolizumab + Ipatasertib
Reporting group description: Atezolizumab (1200 mg IV D1)+ Ipatasertib (400 mg OD D1 – 21)	
Reporting group title	Atezolizumab + Cobimetinib + Bevacizumab
Reporting group description: Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21) + Bevacizumab (10 mg/kg IV D1)	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: Full analyis set of full trial population	

Primary: Proportion of patients with a two-fold increase in GzmB+ CD8+ T cell levels

End point title	Proportion of patients with a two-fold increase in GzmB+ CD8+ T cell levels
End point description: To determine whether adding immune-modulatory agents to atezolizumab increases the probability of an immune response over atezolizumab alone in patients with operable ER+ breast cancer. Proportion of patients with a two-fold increase in GzmB+ CD8+ T cell levels.	
End point type	Primary
End point timeframe: baseline to end of treatment sample	

End point values	Atezolizumab only	Atezolizumab + Cobimetinib	Atezolizumab + Ipatasertib	Atezolizumab + Cobimetinib + Bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[1]	6[2]	18[3]	6[4]
Units: percent				
number (confidence interval 95%)	71.43 (47.82 to 88.72)	66.67 (22.28 to 95.67)	44.44 (21.53 to 69.24)	33.33 (4.33 to 77.72)

Notes:

[1] - Based on tissue for pre and post treatment available for immunohistochemistry.

[2] - Based on tissue for pre and post treatment available for immunohistochemistry.

[3] - Based on tissue for pre and post treatment available for immunohistochemistry.

[4] - Based on tissue for pre and post treatment available for immunohistochemistry.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	51[5]			

Units: percent				
number (confidence interval 95%)	56.68 (42.25 to 70.65)			

Notes:

[5] - Based on tissue for pre and post treatment available for immunohistochemistry.

Statistical analyses

Statistical analysis title	Proportion of patients

Statistical analysis description:

Changes in GzmB+ CD8+ T cell levels was assessed by a central laboratory, comparing tumour samples taken from the pre- to end of study-treatment samples. The proportion of patients with a two-fold increase in GzmB+ CD8+ T cell level is presented here.

Comparison groups	Atezolizumab + Cobimetinib + Bevacizumab v Atezolizumab only
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Odds ratio (OR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0069
upper limit	1.1863

Secondary: Geometric mean Ki67 suppression

End point title	Geometric mean Ki67 suppression

End point description:

The effect of CIT combinations and Atezolizumab alone from pre- and end of study-treatment samples in patients who received at least one dose of study treatment was assessed by a central laboratory. Geometric mean Ki67 suppression is presented. Geometric mean Ki67 suppression is calculated as 1 minus the back-transformation of the arithmetic mean of [ln(Ki67post) – ln(Ki67pre)].

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Atezolizumab only	Atezolizumab + Cobimetinib	Atezolizumab + Ipatasertib	Atezolizumab + Cobimetinib + Bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	8	23	8
Units: cells				
arithmetic mean (confidence interval 95%)	0.019 (-0.153 to 0.1666)	0.025 (-0.538 to 0.382)	-0.14 (-0.585 to 0.179)	0.423 (-0.359 to 0.755)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: cells				
arithmetic mean (confidence interval 95%)	0.035 (-0.14 to 0.184)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean caspase-3 suppression

End point title	Geometric mean caspase-3 suppression

End point description:

Geometric mean EOT Caspase-3 expression is calculated as the back-transformation of the arithmetic mean of [ln(Caspase-3post)]

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	Atezolizumab only	Atezolizumab + Cobimetinib	Atezolizumab + Ipatasertib	Atezolizumab + Cobimetinib + Bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	8	23	8
Units: cells				
number (confidence interval 95%)	-0.465 (-1.778 to 0.227)	-3.338 (-22.116 to 0.166)	-0.346 (-2.404 to 0.467)	-1.038 (-6.608 to 0.453)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: cells				
number (confidence interval 95%)	-0.713 (-1.689 to -0.0915)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to safety visit 135 days after last dose of atezolizumab	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	Atezolizumab only
Reporting group description: Control arm. Atezolizumab (1200 mg IV D1) .	
Reporting group title	Atezolizumab + Cobimetinib
Reporting group description: Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21)	
Reporting group title	Atezolizumab + Ipatasertib
Reporting group description: Atezolizumab (1200 mg IV D1)+ Ipatasertib (400 mg OD D1 – 21)	
Reporting group title	Atezolizumab + Cobimetinib + Bevacizumab
Reporting group description: Atezolizumab (1200 mg IV D1) + Cobimetinib (60 mg PO D1 - 21) + Bevacizumab (10 mg/kg IV D1)	

Serious adverse events	Atezolizumab only	Atezolizumab + Cobimetinib	Atezolizumab + Ipatasertib
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 27 (33.33%)	4 / 9 (44.44%)	14 / 27 (51.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
thromboembolic event			
subjects affected / exposed	1 / 27 (3.70%)	0 / 9 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	0 / 27 (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
Palpitations			

subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	0 / 27 (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	4 / 27 (14.81%)	3 / 9 (33.33%)	4 / 27 (14.81%)
occurrences causally related to treatment / all	3 / 4	3 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	4 / 27 (14.81%)	0 / 9 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 9 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	0 / 27 (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
Colitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	7 / 27 (25.93%)
occurrences causally related to treatment / all	0 / 0	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	0 / 27 (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
Infections and infestations			
Port Infection			
subjects affected / exposed	1 / 27 (3.70%)	0 / 9 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningoencephalitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 9 (11.11%)	0 / 27 (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
Encephalitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 9 (11.11%)	0 / 27 (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
Pneumonia			

subjects affected / exposed	0 / 27 (0.00%)	0 / 9 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Atezolizumab + Cobimetinib + Bevacizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
thromboembolic event			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vestibular neuronitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Pyelonephritis			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Port Infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningoencephalitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Atezolizumab only	Atezolizumab + Cobimetinib	Atezolizumab + Ipatasertib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 27 (96.30%)	9 / 9 (100.00%)	22 / 27 (81.48%)
Investigations			
Haemoglobin increased			
subjects affected / exposed	9 / 27 (33.33%)	6 / 9 (66.67%)	11 / 27 (40.74%)
occurrences (all)	9	6	11
General disorders and administration site conditions			
Rash			
subjects affected / exposed	1 / 27 (3.70%)	1 / 9 (11.11%)	9 / 27 (33.33%)
occurrences (all)	1	1	9

Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	26 / 27 (96.30%) 26	9 / 9 (100.00%) 9	9 / 27 (33.33%) 9

Non-serious adverse events	Atezolizumab + Cobimetinib + Bevacizumab		
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 8 (75.00%)		
Investigations Haemoglobin increased subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
General disorders and administration site conditions Rash subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	5 / 8 (62.50%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2018	1) Addition of optional stool sample collection 2) Change in statistician 3) Updated IBs 4) Changes to Protocol and PISICF post urgent safety measure
23 January 2019	Temporary halt and lift in randomisation due to notification of an immune related meningoencephalitis event that occurred in a South Korean patient randomised into the atezolizumab plus cobimetinib arm. The ECLIPSE TSC discussed this event and felt that although this is a serious event it did not at this stage warrant stopping the trial or amending its design. This was to inform authorities of the event and the steps taken during a temporary halt.
07 March 2019	Amendment only submitted in Germany to add EU Sponsor representative.
28 March 2019	Updated IBs and additional safety information for Protocol v4.0.
30 August 2019	Urgent safety measure. Protocol amendment to remove the Cobimetinib containing arms. Following an Urgent Safety Measure (USM), recruitment in the two cobimetinib arms was permanently discontinued. Patients were subsequently randomised in a 1:1 ratio to receive either atezolizumab alone or atezolizumab plus ipatasertib.
15 October 2020	Updated IBs (Atezolizumab IB v15 and Addendum 2 and Ipatasertib IB v11) and additional safety information for Protocol v6.0 and PIS/ICF v7.0.
23 February 2022	Recruitment end with the view to submit an early termination form once all visits have been completed due to slow recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

23 January 2019	Following a notification of an immune related meningoencephalitis event that occurred in a South Korean patient randomised into the atezolizumab plus cobimetinib arm. This event was notified as a SUSAR to the relevant competent authorities and ethics committees. As per the atezolizumab IB, immune related meningoencephalitis is a known but rare side effect of atezolizumab. However, as in this case atezolizumab was combined with cobimetinib, it was felt this should be investigated further whether the combination exacerbated this known side effect. As a pre-cautionary immediate step we notified participating centres not to consent and randomise any new patients into the study (23 January 2019). The Trial Steering Committee, which also has DMC responsibilities, approved this decision. Discussions with the IMP manufacturer was subsequently held who informed us that there is no signal in their unpublished safety data from other trials investigating the same combination. We also looked into all safety data across all four of the ECLIPSE treatment arms and did not identify any signals that affect the benefit-risk assessment of this trial. The ECLIPSE TSC discussed this event and felt that although this is a serious event it did not warrant stopping the trial or amending its design. The Committee felt that more prominent guidance should be provided to participating investigators on identifying early signs of immune related meningoencephalitis to allow them to treat these patients immediately. A letter was sent out to investigators as per the TSC's recommendations.	25 March 2019

Notes:

Limitations and caveats

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

Early closure of the cobimetinib arm after 17 patients recruited into these arms has meant smaller numbers available for analysis. Covid-19 also had a significant impact on recruitment to the ECLIPSE study and the study closed to recruitment early.

Notes: