Clinical trial results:
A Phase III, Double-blind, Placebo-controlled, Randomized Study of Ipatasertib in Combination with Atezolizumab and Paclitaxel as a Treatment for Patients with Locally Advanced Unresectable or Metastatic Triple-Negative Breast Cancer

Summary

EudraCT number	2019-000810-12
Trial protocol	CZ FR AT PL PT IE ES FI HU BE GR BG DK RO IT
Global end of trial date	28 February 2023

Results information

Result version number	v1 (current)
This version publication date	13 March 2024
First version publication date	13 March 2024

Trial information

Trial identification

Sponsor protocol code	CO41101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04177108
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, CH +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, CH +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	28 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy and safety of ipatasertib in combination with atezolizumab and paclitaxel in locally advanced or metastatic Triple-Negative Breast Cancer (TNBC) previously untreated in this setting.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2019
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	Argentina: 13
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Costa Rica: 3
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Hong Kong: 5
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Japan: 6

Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Peru: 12
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Thailand: 10
Country: Number of subjects enrolled	Türkiye: 9
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Ukraine: 13
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	242
EEA total number of subjects	71

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)	201
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 215 investigative centers from 25 November 2019 to 28 February 2023.

Pre-assignment

Screening details:

A total of 242 participants with Advanced TNBC were enrolled, of which 127 participants were randomised to cohort 1 {programmed death-ligand 1 (PD-L1) Non-positive} and 115 participants to cohort 2 (PD-L1 positive).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel

Arm description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 milligrams per meter square (mg/m^2), intravenous (IV) infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, orally (PO), once daily (QD), from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

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

Dosage and administration details:

Ipatasertib will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details:

Paclitaxel will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details:

Atezolizumab will be administered as per the dosage regimen mentioned in arm descriptions.

Arm title	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel

Arm description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion

on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

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

Dosage and administration details:

Ipatasertib will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details:

Atezolizumab matching placebo will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details:

Paclitaxel will be administered as per the dosage regimen mentioned in arm descriptions.

Arm title	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel

Arm description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

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

Dosage and administration details:

Ipatasertib matching placebo will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details:

Atezolizumab matching placebo will be administered as per the dosage regimen mentioned in arm descriptions.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel will be administered as per the dosage regimen mentioned in arm descriptions.

Arm title	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel

Arm description:

TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

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

Dosage and administration details:

Ipatasertib will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details:

Paclitaxel will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details:

Atezolizumab will be administered as per the dosage regimen mentioned in arm descriptions.

Arm title	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel

Arm description:

TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

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

Dosage and administration details:

Ipatasertib matching placebo will be administered as per the dosage regimen mentioned in arm descriptions.

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

Dosage and administration details: Atezolizumab will be administered as per the dosage regimen mentioned in arm descriptions.	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Paclitaxel will be administered as per the dosage regimen mentioned in arm descriptions.	

Number of subjects in period 1	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel
Started	43	43	41
Completed	0	0	0
Not completed	43	43	41
Adverse event, serious fatal	16	19	13
Physician decision	23	15	18
Consent withdrawn by subject	4	8	9
Reason Not Specified	-	1	-
Lost to follow-up	-	-	1

Number of subjects in period 1	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel
Started	58	57
Completed	0	0
Not completed	58	57
Adverse event, serious fatal	17	18
Physician decision	29	23
Consent withdrawn by subject	11	13
Reason Not Specified	-	2
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel
Reporting group description:	
TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 milligrams per meter square (mg/m^2), intravenous (IV) infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, orally (PO), once daily (QD), from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.	
Reporting group title	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel
Reporting group description:	
TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.	
Reporting group title	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel
Reporting group description:	
TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.	
Reporting group title	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel
Reporting group description:	
TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.	
Reporting group title	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel
Reporting group description:	
TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.	

Reporting group values	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel
Number of subjects	43	43	41
Age categorical Units: participants			
Age Continuous Units: years			
arithmetic mean	55.5	50.8	53.5
standard deviation	± 11.7	± 11.6	± 10.7
Sex/Gender, Customized Units: participants			
Female	43	43	41
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	3	1

Asian	10	7	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	0
White	26	29	29
More than one race	0	0	1
Unknown or Not Reported	0	2	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8	9	6
Not Hispanic or Latino	32	32	35
Unknown or Not Reported	3	2	0

Reporting group values	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel	Total
Number of subjects	58	57	242
Age categorical Units: participants			
Age Continuous Units: years			
arithmetic mean	53.7	51.1	
standard deviation	± 12.1	± 11.7	-
Sex/Gender, Customized Units: participants			
Female	58	57	242
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	6	20
Asian	19	16	61
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	8
White	29	32	145
More than one race	0	1	2
Unknown or Not Reported	3	0	6
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	14	52
Not Hispanic or Latino	41	43	183
Unknown or Not Reported	2	0	7

End points

End points reporting groups

Reporting group title	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 milligrams per meter square (mg/m^2), intravenous (IV) infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, orally (PO), once daily (QD), from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Primary: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

End point title	Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression as determined locally by RECIST or death from any cause during treatment, whichever occurs first. Intent-to-Treat (ITT) population included all participants randomised in this study.

End point type	Primary

End point timeframe:

From Randomisation to disease progression, study completion, or death (up to 39 months)

End point values	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	43	41	58
Units: months				
median (confidence interval 95%)	7.1 (5.1 to 9.3)	5.6 (3.7 to 8.2)	3.7 (3.6 to 5.4)	5.6 (5.4 to 9.2)

End point values	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: months				
median (confidence interval 95%)	5.7 (4.0 to 9.1)			

Statistical analyses

Statistical analysis title	Cohort 1 Arm A Versus Cohort 1 Arm C
Comparison groups	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel v Cohort 1 Arm C: Placebo + Placebo + Paclitaxel
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0098
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.85

Statistical analysis title	Cohort 2 Arm A Versus Cohort 2 Arm B
Comparison groups	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel v Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9809
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.58

Statistical analysis title	Cohort 1 Arm B Versus Cohort 1 Arm C
Comparison groups	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel v Cohort 1 Arm C: Placebo + Placebo + Paclitaxel
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2396
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.25

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomisation to the time of death from any cause on study. Here, 99999 indicates that median and upper limit of 95% confidence interval (CI) could not be calculated due to insufficient number of participants with events. ITT population included all participants randomised in this study.

End point type	Primary

End point timeframe:

From randomization up to study completion or death (Up to 39 months)

End point values	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	43	41	58
Units: months				
median (confidence interval 95%)	15.7 (12.5 to 99999)	15.3 (15.3 to 99999)	16.6 (9.6 to 99999)	99999 (14.1 to 99999)

End point values	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: months				
median (confidence interval 95%)	17.2 (13.4 to 99999)			

Statistical analyses

Statistical analysis title	Cohort 1 Arm A Versus Cohort 1 Arm C
Comparison groups	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel v Cohort 1 Arm C: Placebo + Placebo + Paclitaxel
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6805
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.51

Statistical analysis title	Cohort 2 Arm A Versus Cohort 2 Arm B
Comparison groups	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel v Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9164
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	2.06

Statistical analysis title	Cohort 1 Arm B Versus Cohort 1 Arm C
Comparison groups	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel v Cohort 1

	Arm C: Placebo + Placebo + Paclitaxel
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6314
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.64

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety-evaluable population included all randomised participants who took at least one dose of the study treatment.

End point type	Secondary

End point timeframe:

Up to 39 months

End point values	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	43	41	58
Units: participants	42	43	40	58

End point values	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: participants	56			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 39 months

Adverse event reporting additional description:

Safety-evaluable population included all randomized participants who took at least one dose of the study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 milligrams per meter square (mg/m^2), intravenous (IV) infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, orally (PO), once daily (QD), from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, 400 mg, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab, 840 mg, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Reporting group title	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel

Reporting group description:

TNBC participants with PD-L1 non-positive received a combination of paclitaxel, 80 mg/m^2, IV infusion on Days 1, 8, and 15 of each 28-day cycle and ipatasertib-matching placebo, PO, QD, from Day 1 to Day 21 of each 28-day cycle and atezolizumab-matching placebo, IV infusion on Day 1 and 15 of each 28-day cycle until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurred first.

Serious adverse events	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 43 (32.56%)	7 / 43 (16.28%)	9 / 57 (15.79%)

number of deaths (all causes)	16	19	18
number of deaths resulting from adverse events	3	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (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
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Death			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Pulmonary embolism			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (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
Vocal cord atrophy			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Radius fracture			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Cardiac failure			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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			
Facial paralysis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paresis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Neutropenia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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 disorders			
Diarrhoea			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Abdominal pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Eczema			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Rash			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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			
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Lymphangitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Pneumonia viral			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cholecystitis infective			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Cellulitis			
subjects affected / exposed	2 / 43 (4.65%)	0 / 43 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 43 (4.65%)	0 / 43 (0.00%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Lung abscess			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			

subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (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
Clostridium colitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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
Sepsis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Urinary tract infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	0 / 57 (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 infection			

subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Hyperglycaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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
Hyponatraemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 43 (0.00%)	0 / 57 (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

Serious adverse events	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 58 (27.59%)	7 / 41 (17.07%)	
number of deaths (all causes)	18	13	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord atrophy			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 58 (3.45%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	2 / 58 (3.45%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Pelvic fracture			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 58 (3.45%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Drug eruption			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 58 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			

subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (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 / 58 (0.00%)	0 / 41 (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 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (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			
Dehydration			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Cohort 1 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm B: Ipatasertib + Placebo + Paclitaxel	Cohort 2 Arm B: Placebo+ Atezolizumab + Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 43 (97.67%)	42 / 43 (97.67%)	55 / 57 (96.49%)
Vascular disorders			
Lymphoedema			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	3	1	1
Hypertension			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 43 (20.93%)	6 / 43 (13.95%)	5 / 57 (8.77%)
occurrences (all)	10	8	5
Pain			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	2	1	3
Fatigue			
subjects affected / exposed	8 / 43 (18.60%)	10 / 43 (23.26%)	11 / 57 (19.30%)
occurrences (all)	12	12	11
Pyrexia			
subjects affected / exposed	6 / 43 (13.95%)	3 / 43 (6.98%)	7 / 57 (12.28%)
occurrences (all)	6	5	8
Mucosal inflammation			

subjects affected / exposed	6 / 43 (13.95%)	3 / 43 (6.98%)	6 / 57 (10.53%)
occurrences (all)	7	3	7
Oedema			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	2 / 57 (3.51%)
occurrences (all)	0	1	2
Illness			
subjects affected / exposed	3 / 43 (6.98%)	0 / 43 (0.00%)	0 / 57 (0.00%)
occurrences (all)	9	0	0
Malaise			
subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	2 / 57 (3.51%)
occurrences (all)	0	2	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 43 (9.30%)	5 / 43 (11.63%)	3 / 57 (5.26%)
occurrences (all)	4	5	4
Dyspnoea			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	3 / 57 (5.26%)
occurrences (all)	3	3	3
Rhinorrhoea			
subjects affected / exposed	4 / 43 (9.30%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	4	1	1
Epistaxis			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	3	1	1
Pneumonitis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	0	0	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 43 (9.30%)	6 / 43 (13.95%)	4 / 57 (7.02%)
occurrences (all)	4	6	4
Anxiety			

subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	0	0	1
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 43 (2.33%)	6 / 43 (13.95%)	0 / 57 (0.00%)
occurrences (all)	1	14	0
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 43 (11.63%)	6 / 43 (13.95%)	1 / 57 (1.75%)
occurrences (all)	7	9	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 43 (9.30%)	2 / 43 (4.65%)	1 / 57 (1.75%)
occurrences (all)	5	4	1
Weight decreased			
subjects affected / exposed	4 / 43 (9.30%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	4	0	1
Neutrophil count decreased			
subjects affected / exposed	5 / 43 (11.63%)	9 / 43 (20.93%)	6 / 57 (10.53%)
occurrences (all)	12	14	16
Lymphocyte count decreased			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	16	9	1
Lipase increased			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	4	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 43 (16.28%)	10 / 43 (23.26%)	10 / 57 (17.54%)
occurrences (all)	9	14	18
Blood creatinine increased			
subjects affected / exposed	5 / 43 (11.63%)	2 / 43 (4.65%)	1 / 57 (1.75%)
occurrences (all)	7	2	2
White blood cell count decreased			
subjects affected / exposed	5 / 43 (11.63%)	6 / 43 (13.95%)	2 / 57 (3.51%)
occurrences (all)	13	14	10
Alanine aminotransferase increased			

subjects affected / exposed	11 / 43 (25.58%)	11 / 43 (25.58%)	11 / 57 (19.30%)
occurrences (all)	15	12	18
Blood albumin decreased			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	0 / 57 (0.00%)
occurrences (all)	2	2	0
Amylase increased			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	2 / 57 (3.51%)
occurrences (all)	0	0	2
Blood cholesterol increased			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	2 / 57 (3.51%)
occurrences (all)	1	4	3
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	1 / 57 (1.75%)
occurrences (all)	0	4	1
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	0 / 57 (0.00%)
occurrences (all)	1	2	0
Blood glucose increased			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	0 / 57 (0.00%)
occurrences (all)	2	4	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 43 (2.33%)	4 / 43 (9.30%)	1 / 57 (1.75%)
occurrences (all)	1	5	1
Infusion related reaction			
subjects affected / exposed	3 / 43 (6.98%)	1 / 43 (2.33%)	5 / 57 (8.77%)
occurrences (all)	5	2	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 43 (9.30%)	4 / 43 (9.30%)	4 / 57 (7.02%)
occurrences (all)	4	4	4
Headache			
subjects affected / exposed	2 / 43 (4.65%)	6 / 43 (13.95%)	12 / 57 (21.05%)
occurrences (all)	2	6	14
Dysgeusia			

subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	2 / 57 (3.51%)
occurrences (all)	0	1	2
Neuropathy peripheral			
subjects affected / exposed	15 / 43 (34.88%)	8 / 43 (18.60%)	8 / 57 (14.04%)
occurrences (all)	19	9	9
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 43 (9.30%)	6 / 43 (13.95%)	9 / 57 (15.79%)
occurrences (all)	4	7	10
Polyneuropathy			
subjects affected / exposed	2 / 43 (4.65%)	3 / 43 (6.98%)	0 / 57 (0.00%)
occurrences (all)	2	3	0
Paraesthesia			
subjects affected / exposed	5 / 43 (11.63%)	3 / 43 (6.98%)	1 / 57 (1.75%)
occurrences (all)	6	3	1
Syncope			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	0	0	1
Neurotoxicity			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	2 / 57 (3.51%)
occurrences (all)	1	1	2
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 43 (9.30%)	2 / 43 (4.65%)	4 / 57 (7.02%)
occurrences (all)	5	2	7
Anaemia			
subjects affected / exposed	15 / 43 (34.88%)	7 / 43 (16.28%)	12 / 57 (21.05%)
occurrences (all)	22	18	17
Neutropenia			
subjects affected / exposed	15 / 43 (34.88%)	5 / 43 (11.63%)	9 / 57 (15.79%)
occurrences (all)	21	21	19
Lymphopenia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	0 / 43 (0.00%)	1 / 43 (2.33%)	3 / 57 (5.26%)
occurrences (all)	0	1	3
Stomatitis			
subjects affected / exposed	3 / 43 (6.98%)	6 / 43 (13.95%)	3 / 57 (5.26%)
occurrences (all)	3	7	4
Dyspepsia			
subjects affected / exposed	3 / 43 (6.98%)	3 / 43 (6.98%)	0 / 57 (0.00%)
occurrences (all)	4	3	0
Vomiting			
subjects affected / exposed	7 / 43 (16.28%)	10 / 43 (23.26%)	8 / 57 (14.04%)
occurrences (all)	16	14	9
Abdominal pain upper			
subjects affected / exposed	5 / 43 (11.63%)	0 / 43 (0.00%)	3 / 57 (5.26%)
occurrences (all)	7	0	3
Abdominal pain			
subjects affected / exposed	2 / 43 (4.65%)	4 / 43 (9.30%)	2 / 57 (3.51%)
occurrences (all)	2	4	2
Diarrhoea			
subjects affected / exposed	32 / 43 (74.42%)	30 / 43 (69.77%)	16 / 57 (28.07%)
occurrences (all)	66	71	28
Nausea			
subjects affected / exposed	17 / 43 (39.53%)	14 / 43 (32.56%)	13 / 57 (22.81%)
occurrences (all)	21	16	16
Constipation			
subjects affected / exposed	7 / 43 (16.28%)	12 / 43 (27.91%)	24 / 57 (42.11%)
occurrences (all)	7	16	33
Gastritis			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	1 / 57 (1.75%)
occurrences (all)	1	1	1
Dry mouth			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences (all)	1	1	0
Abdominal discomfort			
subjects affected / exposed	3 / 43 (6.98%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	3	0	1
Gastrooesophageal reflux disease			

subjects affected / exposed	3 / 43 (6.98%)	2 / 43 (4.65%)	0 / 57 (0.00%)
occurrences (all)	5	2	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 43 (0.00%)	0 / 57 (0.00%)
occurrences (all)	4	0	0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	3 / 57 (5.26%)
occurrences (all)	2	2	3
Pruritus			
subjects affected / exposed	3 / 43 (6.98%)	0 / 43 (0.00%)	8 / 57 (14.04%)
occurrences (all)	4	0	8
Urticaria			
subjects affected / exposed	4 / 43 (9.30%)	0 / 43 (0.00%)	3 / 57 (5.26%)
occurrences (all)	4	0	3
Alopecia			
subjects affected / exposed	10 / 43 (23.26%)	13 / 43 (30.23%)	25 / 57 (43.86%)
occurrences (all)	10	13	26
Rash maculo-papular			
subjects affected / exposed	1 / 43 (2.33%)	4 / 43 (9.30%)	0 / 57 (0.00%)
occurrences (all)	1	5	0
Rash			
subjects affected / exposed	10 / 43 (23.26%)	10 / 43 (23.26%)	17 / 57 (29.82%)
occurrences (all)	11	15	35
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 43 (0.00%)	0 / 43 (0.00%)	4 / 57 (7.02%)
occurrences (all)	0	0	5
Hypothyroidism			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	6 / 57 (10.53%)
occurrences (all)	2	2	7
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 43 (6.98%)	4 / 43 (9.30%)	5 / 57 (8.77%)
occurrences (all)	3	5	6

Arthralgia			
subjects affected / exposed	4 / 43 (9.30%)	4 / 43 (9.30%)	4 / 57 (7.02%)
occurrences (all)	4	5	9
Bone pain			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	1 / 57 (1.75%)
occurrences (all)	2	3	2
Musculoskeletal pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	5 / 43 (11.63%)	3 / 43 (6.98%)	5 / 57 (8.77%)
occurrences (all)	5	3	5
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 43 (6.98%)	4 / 43 (9.30%)	2 / 57 (3.51%)
occurrences (all)	3	4	3
COVID-19			
subjects affected / exposed	2 / 43 (4.65%)	2 / 43 (4.65%)	3 / 57 (5.26%)
occurrences (all)	2	2	3
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 43 (2.33%)	3 / 43 (6.98%)	1 / 57 (1.75%)
occurrences (all)	4	3	1
Decreased appetite			
subjects affected / exposed	6 / 43 (13.95%)	6 / 43 (13.95%)	7 / 57 (12.28%)
occurrences (all)	7	6	9
Hyperkalaemia			
subjects affected / exposed	1 / 43 (2.33%)	1 / 43 (2.33%)	3 / 57 (5.26%)
occurrences (all)	1	1	4
Hypertriglyceridaemia			
subjects affected / exposed	0 / 43 (0.00%)	5 / 43 (11.63%)	1 / 57 (1.75%)
occurrences (all)	0	11	1
Hypokalaemia			
subjects affected / exposed	4 / 43 (9.30%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	6	0	1
Hyperglycaemia			

subjects affected / exposed	10 / 43 (23.26%)	4 / 43 (9.30%)	3 / 57 (5.26%)
occurrences (all)	12	9	4
Hyponatraemia			
subjects affected / exposed	2 / 43 (4.65%)	1 / 43 (2.33%)	0 / 57 (0.00%)
occurrences (all)	2	1	0
Hypomagnesaemia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 43 (0.00%)	1 / 57 (1.75%)
occurrences (all)	3	0	1
Hypernatraemia			
subjects affected / exposed	1 / 43 (2.33%)	2 / 43 (4.65%)	0 / 57 (0.00%)
occurrences (all)	2	2	0
Dehydration			
subjects affected / exposed	0 / 43 (0.00%)	2 / 43 (4.65%)	0 / 57 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Cohort 2 Arm A: Ipatasertib + Atezolizumab + Paclitaxel	Cohort 1 Arm C: Placebo + Placebo + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 58 (96.55%)	40 / 41 (97.56%)	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	4 / 58 (6.90%)	2 / 41 (4.88%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 58 (22.41%)	7 / 41 (17.07%)	
occurrences (all)	24	9	
Pain			
subjects affected / exposed	3 / 58 (5.17%)	3 / 41 (7.32%)	
occurrences (all)	3	4	
Oedema peripheral			
subjects affected / exposed	4 / 58 (6.90%)	4 / 41 (9.76%)	
occurrences (all)	5	6	

Fatigue			
subjects affected / exposed	14 / 58 (24.14%)	5 / 41 (12.20%)	
occurrences (all)	15	8	
Pyrexia			
subjects affected / exposed	7 / 58 (12.07%)	1 / 41 (2.44%)	
occurrences (all)	10	2	
Mucosal inflammation			
subjects affected / exposed	4 / 58 (6.90%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
Oedema			
subjects affected / exposed	4 / 58 (6.90%)	0 / 41 (0.00%)	
occurrences (all)	4	0	
Illness			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	3 / 58 (5.17%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	3 / 58 (5.17%)	4 / 41 (9.76%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 58 (6.90%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
Dyspnoea			
subjects affected / exposed	5 / 58 (8.62%)	4 / 41 (9.76%)	
occurrences (all)	5	4	
Rhinorrhoea			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 58 (1.72%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Pneumonitis			

subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 58 (10.34%)	3 / 41 (7.32%)	
occurrences (all)	6	3	
Anxiety			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 58 (5.17%)	1 / 41 (2.44%)	
occurrences (all)	7	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 58 (10.34%)	1 / 41 (2.44%)	
occurrences (all)	9	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 58 (10.34%)	0 / 41 (0.00%)	
occurrences (all)	7	0	
Weight decreased			
subjects affected / exposed	3 / 58 (5.17%)	1 / 41 (2.44%)	
occurrences (all)	3	2	
Neutrophil count decreased			
subjects affected / exposed	9 / 58 (15.52%)	5 / 41 (12.20%)	
occurrences (all)	20	7	
Lymphocyte count decreased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	10	0	
Lipase increased			
subjects affected / exposed	5 / 58 (8.62%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 58 (18.97%)	10 / 41 (24.39%)	
occurrences (all)	16	18	
Blood creatinine increased			

subjects affected / exposed	5 / 58 (8.62%)	0 / 41 (0.00%)	
occurrences (all)	8	0	
White blood cell count decreased			
subjects affected / exposed	4 / 58 (6.90%)	1 / 41 (2.44%)	
occurrences (all)	11	2	
Alanine aminotransferase increased			
subjects affected / exposed	12 / 58 (20.69%)	12 / 41 (29.27%)	
occurrences (all)	19	15	
Blood albumin decreased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	6	0	
Amylase increased			
subjects affected / exposed	4 / 58 (6.90%)	0 / 41 (0.00%)	
occurrences (all)	4	0	
Blood cholesterol increased			
subjects affected / exposed	4 / 58 (6.90%)	2 / 41 (4.88%)	
occurrences (all)	9	2	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Glycosylated haemoglobin increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Blood glucose increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 58 (5.17%)	1 / 41 (2.44%)	
occurrences (all)	8	1	
Infusion related reaction			
subjects affected / exposed	8 / 58 (13.79%)	2 / 41 (4.88%)	
occurrences (all)	11	2	
Nervous system disorders			

Dizziness			
subjects affected / exposed	5 / 58 (8.62%)	2 / 41 (4.88%)	
occurrences (all)	5	11	
Headache			
subjects affected / exposed	11 / 58 (18.97%)	3 / 41 (7.32%)	
occurrences (all)	15	3	
Dysgeusia			
subjects affected / exposed	7 / 58 (12.07%)	3 / 41 (7.32%)	
occurrences (all)	8	3	
Neuropathy peripheral			
subjects affected / exposed	8 / 58 (13.79%)	10 / 41 (24.39%)	
occurrences (all)	8	11	
Peripheral sensory neuropathy			
subjects affected / exposed	11 / 58 (18.97%)	5 / 41 (12.20%)	
occurrences (all)	11	6	
Polyneuropathy			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	4 / 58 (6.90%)	3 / 41 (7.32%)	
occurrences (all)	5	3	
Syncope			
subjects affected / exposed	3 / 58 (5.17%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Neurotoxicity			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	8 / 58 (13.79%)	2 / 41 (4.88%)	
occurrences (all)	13	6	
Anaemia			
subjects affected / exposed	22 / 58 (37.93%)	6 / 41 (14.63%)	
occurrences (all)	36	10	
Neutropenia			

subjects affected / exposed	11 / 58 (18.97%)	8 / 41 (19.51%)	
occurrences (all)	36	26	
Lymphopenia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 58 (5.17%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Stomatitis			
subjects affected / exposed	7 / 58 (12.07%)	2 / 41 (4.88%)	
occurrences (all)	8	3	
Dyspepsia			
subjects affected / exposed	6 / 58 (10.34%)	2 / 41 (4.88%)	
occurrences (all)	8	2	
Vomiting			
subjects affected / exposed	8 / 58 (13.79%)	0 / 41 (0.00%)	
occurrences (all)	10	0	
Abdominal pain upper			
subjects affected / exposed	5 / 58 (8.62%)	2 / 41 (4.88%)	
occurrences (all)	7	2	
Abdominal pain			
subjects affected / exposed	4 / 58 (6.90%)	4 / 41 (9.76%)	
occurrences (all)	5	4	
Diarrhoea			
subjects affected / exposed	37 / 58 (63.79%)	15 / 41 (36.59%)	
occurrences (all)	81	22	
Nausea			
subjects affected / exposed	22 / 58 (37.93%)	9 / 41 (21.95%)	
occurrences (all)	36	10	
Constipation			
subjects affected / exposed	16 / 58 (27.59%)	26 / 41 (63.41%)	
occurrences (all)	22	29	
Gastritis			
subjects affected / exposed	1 / 58 (1.72%)	3 / 41 (7.32%)	
occurrences (all)	1	3	

Dry mouth			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Abdominal discomfort			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 58 (3.45%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	8 / 58 (13.79%)	5 / 41 (12.20%)	
occurrences (all)	9	6	
Urticaria			
subjects affected / exposed	0 / 58 (0.00%)	0 / 41 (0.00%)	
occurrences (all)	0	0	
Alopecia			
subjects affected / exposed	18 / 58 (31.03%)	19 / 41 (46.34%)	
occurrences (all)	18	19	
Rash maculo-papular			
subjects affected / exposed	4 / 58 (6.90%)	0 / 41 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	19 / 58 (32.76%)	7 / 41 (17.07%)	
occurrences (all)	27	11	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			

subjects affected / exposed	6 / 58 (10.34%)	0 / 41 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 58 (8.62%)	2 / 41 (4.88%)	
occurrences (all)	7	2	
Arthralgia			
subjects affected / exposed	7 / 58 (12.07%)	3 / 41 (7.32%)	
occurrences (all)	8	3	
Bone pain			
subjects affected / exposed	5 / 58 (8.62%)	2 / 41 (4.88%)	
occurrences (all)	5	2	
Musculoskeletal pain			
subjects affected / exposed	0 / 58 (0.00%)	3 / 41 (7.32%)	
occurrences (all)	0	3	
Myalgia			
subjects affected / exposed	9 / 58 (15.52%)	8 / 41 (19.51%)	
occurrences (all)	26	9	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 58 (5.17%)	2 / 41 (4.88%)	
occurrences (all)	3	8	
COVID-19			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 58 (1.72%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	16 / 58 (27.59%)	6 / 41 (14.63%)	
occurrences (all)	20	7	
Hyperkalaemia			
subjects affected / exposed	2 / 58 (3.45%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Hypertriglyceridaemia			

subjects affected / exposed	5 / 58 (8.62%)	0 / 41 (0.00%)	
occurrences (all)	5	0	
Hypokalaemia			
subjects affected / exposed	6 / 58 (10.34%)	1 / 41 (2.44%)	
occurrences (all)	8	1	
Hyperglycaemia			
subjects affected / exposed	12 / 58 (20.69%)	2 / 41 (4.88%)	
occurrences (all)	18	2	
Hyponatraemia			
subjects affected / exposed	4 / 58 (6.90%)	2 / 41 (4.88%)	
occurrences (all)	5	2	
Hypomagnesaemia			
subjects affected / exposed	1 / 58 (1.72%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Hypernatraemia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	6	0	
Dehydration			
subjects affected / exposed	3 / 58 (5.17%)	0 / 41 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2019	Amendment 1: 1. Disease-specific inclusion criteria was updated to include a criterion that a participant must be an appropriate candidate for paclitaxel monotherapy if tumor PD-L1 status is unknown and if tumor status is known to be PD-L1 positive, the participant should be an appropriate candidate for atezolizumab+paclitaxel. 2. General exclusion criteria was updated to include a criterion that a participant must not be on current treatment with medications used at doses known to cause clinically relevant prolongation of QT/corrected QT (QTc) interval. 3. Disease-specific exclusion criteria have been updated to include a criterion that a participant must not have known germline breast cancer gene (BRCA)1/2 deleterious mutation. 4. The Optional Interim Analyses section (Section 6.9.3) was removed.
20 September 2019	Amendment 2: 1. Enrolment number was updated from 1150 to 1155 participants, with a change from approximately 520 to approximately 525 participants in Cohort 1. The allocation of participants between arms in Cohort 1 was made equal, to support the independent testing of Arm A vs. Arm C, and Arm B vs. Arm C.
18 August 2020	Amendment 3: 1. The study rationale and benefit-risk assessment was updated to indicate that based on results from the primary analysis of the MO39196 study, the control arm for Cohort 2 of this Study CO41101 (atezolizumab plus paclitaxel plus placebo for ipatasertib) was no longer considered appropriate. As of 6 August 2020, further enrollment in Cohort 2 was suspended, and all participants in Cohort 2 were unblinded to treatment assignment.
21 December 2020	Amendment 4: 1. Section 1.2 was updated to include the outcome of the primary analysis of the CO40016 study and rationale for termination of enrollment and unblinding of Cohort 1 of Study CO41101. 2. Study was updated to indicate that based on results from the primary analysis of the CO40016 study in TNBC, Arm B for Cohort 1 of this Study CO41101 (ipatasertib plus paclitaxel plus placebo for atezolizumab) was no longer considered appropriate. As of 18 September 2020, further enrollment in Cohort 1 was terminated, and all participants in Cohort 1 were unblinded to treatment assignment on 21 September 2020. 3. All secondary efficacy objectives and pharmacokinetic and immunogenicity objectives were moved to exploratory objectives. 4. The total length of the study was changed to 2-3 years.
25 February 2022	Amendment 5: 1. Benefit-risk assessment and guidance on concomitant administration of severe acute respiratory syndrome coronavirus 2 vaccines with atezolizumab was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported