Clinical trial results:
A Double-Blind, Placebo-Controlled, Randomized Phase III Study of Ipatasertib in Combination With Paclitaxel as a Treatment for Patients With PIK3CA/AKT1/PTEN-Altered, Locally Advanced or Metastatic, Triple-Negative Breast Cancer or Hormone Receptor–Positive, HER2-Negative Breast Cancer

Summary

EudraCT number	2017-001548-36
Trial protocol	DE ES GB CZ HU PL BE FR GR SI IT
Global end of trial date	04 January 2023

Results information

Result version number	v1 (current)
This version publication date	18 January 2024
First version publication date	18 January 2024

Trial information

Trial identification

Sponsor protocol code	CO40016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03337724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
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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	04 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to evaluate the efficacy of ipatasertib + paclitaxel versus placebo + paclitaxel in participants with histologically confirmed, locally advanced or metastatic triple-negative breast cancer (TNBC) and in participants with locally advanced or metastatic hormone receptor positive (HR+)/ human epidermal growth factor receptor 2 negative (HER2−) breast adenocarcinoma who are not suitable for endocrine therapy.The study will also assess the efficacy of ipatasertib+atezolizumab+paclitaxel in participants with TNBC, screened for Cohort A but without phosphatidylinositol-4,5-bisphosphate3-kinase,catalytic subunit,alpha(PIK3CA)/serine-threonine kinase(AKT1)/phosphatase and tensin homolog(PTEN)-altered tumor.

Protection of trial subjects:

All study participants were required to read and sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	45 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	North Macedonia: 12
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Brazil: 72
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Costa Rica: 6
Country: Number of subjects enrolled	Mexico: 17
Country: Number of subjects enrolled	Peru: 60

Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Türkiye: 11
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	579
EEA total number of subjects	141

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)	442
From 65 to 84 years	137
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with TNBC or HR+/HER- breast cancer took part in the study in Argentina, Australia, Belgium, Brazil, Canada,Chile, Costa Rica,Czech Republic,France, Greece,Germany, Hungary, Italy, India, Japan,Macedonia,Mexico,Poland,Peru,Korea,Russia,Slovenia,Spain,Singapore,South Africa, Taiwan, Turkey, Ukraine,UK,&USA from 06-01-2018 to 04-01-2023.

Pre-assignment

Screening details:

Participants with TNBC or HR+/HER2- breast adenocarcinoma with PIK3CA/AKT1/PTEN-altered tumor were randomized to ipatasertib 400 mg + paclitaxel or placebo + paclitaxel (Cohorts A,B) & those with TNBC without PIK3CA/ AKT1/PTEN-altered tumor received ipatasertib + atezolizumab +paclitaxel (Cohort C).

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	Investigator, Assessor, Subject

Blinding implementation details:

Cohorts A and B were randomised controlled double-blind and Cohort C was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: Placebo + Paclitaxel

Arm description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 milligram per square meter (mg/m^2), intravenously (IV), on Days 1, 8, and 15 of each 28-day cycle and placebo, orally once a day (QD), on Days 1 to 21 of each 28-day cycle up to 58.9 months.

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

Dosage and administration details:

Placebo administered orally QD on Days 1 to 21 of each 28-day cycle.

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

Dosage and administration details:

Paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle

Arm title	Cohort A: Ipatasertib + Paclitaxel

Arm description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, at a dose of 400 mg, administered orally QD, on

Days 1 to 21 of each 28-day cycle up to 58.9 months.

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:

400 mg administered orally QD on Days 1 to 21 of each 28-day cycle

Arm title	Cohort B: Placebo + Paclitaxel

Arm description:

Participants with histologically confirmed HR+ /HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle and placebo orally QD on Days 1 to 21 of each 28-day cycle up to 59.9 months.

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

Dosage and administration details:

Placebo administered orally QD on Days 1 to 21 of each 28-day cycle.

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

Dosage and administration details:

Paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle

Arm title	Cohort B: Ipatasertib + Paclitaxel

Arm description:

Participants with histologically confirmed HR+/HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle and ipatasertib at a dose of 400 mg administered orally QD on Days 1 to 21 of each 28-day cycle up to 59.9 months.

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:

400 mg administered orally QD on Days 1 to 21 of each 28-day cycle

Arm title	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel

Arm description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC without PIK3CA/AKT1/PTEN-altered tumors and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle, ipatasertib at a dose of 400 mg administered orally QD on Days 1 to 21 of each 28-day cycle, and atezolizumab 840 mg IV on Days 1 and 15 of each 28-day cycle up to 45.5 months.

Arm type	Experimental
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 840 mg IV on Days 1 and 15 of each 28-day cycle	
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 administered orally QD on Days 1 to 21 of each 28-day cycle	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle	

Number of subjects in period 1	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel
Started	87	168	76
Safety Evaluable Population	87	166	75
Completed	0	0	0
Not completed	87	168	76
Physician decision	16	34	14
Adverse Event	1	1	-
Protocol Deviation	-	1	1
Death	40	89	43
Progressive Disease	-	2	1
Withdrawal by Subject	13	15	4
Symptomatic Deterioration	-	-	-
Reason not specified	12	21	9
Lost to follow-up	5	5	4

Number of subjects in period 1	Cohort B: Ipatasertib + Paclitaxel	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel
Started	146	102
Safety Evaluable Population	145	102

Completed	0	0
Not completed	146	102
Physician decision	34	13
Adverse Event	1	-
Protocol Deviation	1	-
Death	76	50
Progressive Disease	2	-
Withdrawal by Subject	15	6
Symptomatic Deterioration	1	-
Reason not specified	9	29
Lost to follow-up	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: Placebo + Paclitaxel
Reporting group description:	
Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 milligram per square meter (mg/m^2), intravenously (IV), on Days 1, 8, and 15 of each 28-day cycle and placebo, orally once a day (QD), on Days 1 to 21 of each 28-day cycle up to 58.9 months.	
Reporting group title	Cohort A: Ipatasertib + Paclitaxel
Reporting group description:	
Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, at a dose of 400 mg, administered orally QD, on Days 1 to 21 of each 28-day cycle up to 58.9 months.	
Reporting group title	Cohort B: Placebo + Paclitaxel
Reporting group description:	
Participants with histologically confirmed HR+ /HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle and placebo orally QD on Days 1 to 21 of each 28-day cycle up to 59.9 months.	
Reporting group title	Cohort B: Ipatasertib + Paclitaxel
Reporting group description:	
Participants with histologically confirmed HR+/HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle and ipatasertib at a dose of 400 mg administered orally QD on Days 1 to 21 of each 28-day cycle up to 59.9 months.	
Reporting group title	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel
Reporting group description:	
Participants with histologically confirmed locally advanced unresectable or metastatic TNBC without PIK3CA/AKT1/PTEN-altered tumors and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle, ipatasertib at a dose of 400 mg administered orally QD on Days 1 to 21 of each 28-day cycle, and atezolizumab 840 mg IV on Days 1 and 15 of each 28-day cycle up to 45.5 months.	

Reporting group values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel
Number of subjects	87	168	76
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	54.2	54.6	54.5
standard deviation	± 12.6	± 12.8	± 11.3
Gender Categorical Units: participants			
Female	87	167	76
Male	0	1	0

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	13	15	3
Asian	17	37	22
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	5	3
White	51	99	45
More than one race	0	4	2
Unknown or Not Reported	5	8	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	29	59	13
Not Hispanic or Latino	57	101	62
Unknown or Not Reported	1	8	1

Reporting group values	Cohort B: Ipatasertib + Paclitaxel	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel	Total
Number of subjects	146	102	579
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	57.2	54.6	
standard deviation	± 11.1	± 11.7	-
Gender Categorical Units: participants			
Female	144	102	576
Male	2	0	3
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	4	5	40
Asian	38	12	126
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	2	9	20
White	93	55	343
More than one race	0	5	11
Unknown or Not Reported	9	15	38
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	29	36	166
Not Hispanic or Latino	115	58	393
Unknown or Not Reported	2	8	20

End points

End points reporting groups

Reporting group title	Cohort A: Placebo + Paclitaxel

Reporting group description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 milligram per square meter (mg/m^2), intravenously (IV), on Days 1, 8, and 15 of each 28-day cycle and placebo, orally once a day (QD), on Days 1 to 21 of each 28-day cycle up to 58.9 months.

Reporting group title	Cohort A: Ipatasertib + Paclitaxel

Reporting group description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, at a dose of 400 mg, administered orally QD, on Days 1 to 21 of each 28-day cycle up to 58.9 months.

Reporting group title	Cohort B: Placebo + Paclitaxel

Reporting group description:

Participants with histologically confirmed HR+ /HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle and placebo orally QD on Days 1 to 21 of each 28-day cycle up to 59.9 months.

Reporting group title	Cohort B: Ipatasertib + Paclitaxel

Reporting group description:

Participants with histologically confirmed HR+/HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle and ipatasertib at a dose of 400 mg administered orally QD on Days 1 to 21 of each 28-day cycle up to 59.9 months.

Reporting group title	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel

Reporting group description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC without PIK3CA/AKT1/PTEN-altered tumors and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day cycle, ipatasertib at a dose of 400 mg administered orally QD on Days 1 to 21 of each 28-day cycle, and atezolizumab 840 mg IV on Days 1 and 15 of each 28-day cycle up to 45.5 months.

Primary: Cohort A: Progression-Free Survival (PFS)

End point title	Cohort A: Progression-Free Survival (PFS)[1]

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression, as determined locally by the investigator through the use of Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1), or death from any cause, whichever occurred first, assessed up to 28 months for this endpoint. Progressive disease (PD) was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeter (mm). ITT Population included all randomized participants in Cohort A regardless of whether the participants received the assigned treatment.

End point type	Primary

End point timeframe:

From randomization up to 27 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort A. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	168		
Units: months				
median (confidence interval 95%)	6.1 (5.5 to 9.0)	7.4 (5.6 to 8.5)		

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)
Comparison groups	Cohort A: Placebo + Paclitaxel v Cohort A: Ipatasertib + Paclitaxel
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.9237
Method	Logrank
Parameter estimate	Stratified Hazard Ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.45

Notes:

[2] - Stratification variables were: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region, tumor PIK3CA/AKT1/PTEN alteration status (PIK3CA/AKT1-activating mutations vs. PTEN alterations with no PIK3CA/AKT1-activating mutations).

Primary: Cohort B: PFS

End point title	Cohort B: PFS[3]

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v.1.1, or death from any cause, whichever occurred first, assessed up to 24.4 months for this outcome measure. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. Abbreviation used in statistical analysis: PI3K=phosphoinositide 3-kinase and mTOR=mammalian target of rapamycin inhibitor. ITT Population included all randomized participants in Cohort B regardless of whether the participants received the assigned treatment.

End point type	Primary

End point timeframe:

From randomization up to 24.4 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	127		
Units: months				
median (confidence interval 95%)	9.3 (7.2 to 12.2)	9.3 (8.0 to 11.0)		

Statistical analyses

Statistical analysis title	Superiority
Comparison groups	Cohort B: Placebo + Paclitaxel v Cohort B: Ipatasertib + Paclitaxel
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.9965
Method	Logrank
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.4

Notes:

[4] - Stratification variables were: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region, prior therapy with a PI3K or mTOR inhibitor (yes vs. no).

Primary: Cohort C: PFS

End point title	Cohort C: PFS[5][6]

End point description:

PFS for cohort C was defined as the time from enrollment to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v.1.1, or death from any cause, whichever occurred first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. ITT population included of all enrolled participants in Cohort C.

End point type	Primary

End point timeframe:

From enrollment up to 31 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No descriptive statistics were planned for this endpoint.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: months				
median (confidence interval 95%)	7.1 (5.5 to 9.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: ORR

End point title	Cohort C: ORR[7]

End point description:

ORR was defined as percentage of participants with PR or CR on 2 consecutive occasions ≥4 weeks apart as determined by the investigator using RECIST v.1.1. CR was defined as the disappearance of all target lesions or any pathological lymph nodes (whether target or non-target) having a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Percentages are rounded off to the nearest decimal point. ITT population consisted of all enrolled participants in Cohort C.

End point type	Secondary

End point timeframe:

From enrollment up to 31 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: percentage of participants				
number (confidence interval 95%)	52.9 (42.80 to 62.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B: Objective Response Rate (ORR)

End point title	Cohort A and B: Objective Response Rate (ORR)[8]

End point description:

ORR was defined as percentage of participants with partial response (PR) or complete response (CR) on 2 consecutive occasions ≥4 weeks apart as determined by the investigator using RECIST v.1.1 assessed up to 28 months for this endpoint. CR was defined as the disappearance of all target lesions or any pathological lymph nodes (LN; whether target or non-target) having a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters(SoD) of target lesions, taking as reference the baseline sum of diameters. Percentages are rounded off to the nearest decimal point. ITT Population included all randomized participants in Cohorts A and B regardless of whether the participants received the assigned treatment. Number analyzed is the number of participants with measurable disease at baseline.

End point type	Secondary

End point timeframe:

From randomization up to 27 months for Cohort A and up to 24.4 months for Cohort B

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only Cohorts A and B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	167	75	144
Units: percentage of participants				
number (confidence interval 95%)	34.9 (24.92 to 45.92)	38.9 (31.49 to 46.76)	46.7 (35.05 to 58.55)	46.5 (38.18 to 55.02)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B: Duration of Response (DOR)

End point title	Cohort A and B: Duration of Response (DOR)[9]

End point description:

DOR= time from the first occurrence of a documented OR (CR or PR) to PD, per investigator per RECIST v1.1,/death from any cause, whichever occurred first assessed up to 28 months for this endpoint. CR=disappearance of all target lesions or any pathological LN (whether target or non-target) having a reduction in short axis to <10 mm. PR=at least a 30% decrease in the SoD of target lesions, taking as reference baseline SoD. PD=at least a 20% increase in SoD of target lesions, taking as reference the smallest sum on study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one/more new lesions was also considered PD. ITT Population (Cohorts A & B) participants. Number analyzed=number of participants with OR i.e.responders.9999= upper limit of 95% confidence interval (CI) was not estimable due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From randomization up to 27 months for Cohort A and up to 24.4 months for Cohort B

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is reporting data for only Cohorts A and B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	65	35	67
Units: months				
median (confidence interval 95%)	16.6 (4.9 to 9999)	9.4 (7.3 to 11.1)	9.2 (6.8 to 12.5)	9.2 (7.2 to 11.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: DOR

End point title	Cohort C: DOR[10]

End point description:

DOR= time from the first occurrence of a documented OR (CR or PR) to PD, per investigator per RECIST v1.1,/death from any cause, whichever occurred first assessed up to 28 months for this endpoint. CR=disappearance of all target lesions or any pathological LN (whether target or non-target) having a reduction in short axis to <10 mm. PR=at least a 30% decrease in the SoD of target lesions, taking as reference baseline SoD. PD=at least a 20% increase in SoD of target lesions, taking as reference the smallest sum on study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one/more new lesions was also considered PD. ITT Population (Cohorts C) participants. Number analyzed=number of participants with OR i.e.responders.9999= upper limit of 95% confidence interval (CI) was not estimable due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From enrollment up to 31 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	54			
Units: months				
median (confidence interval 95%)	8.77 (5.7 to 12.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B: Clinical Benefit Rate (CBR)

End point title	Cohort A and B: Clinical Benefit Rate (CBR)

End point description:

CBR was defined as percentage of participants with an objective response (CR or PR), or stable disease (SD) for at least 24 weeks, as determined by the investigator through the use of RECIST v.1.1 assessed up to 28 months for this endpoint.CR was defined as the disappearance of all target lesions or any pathological lymph nodes (whether target or non-target) having a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Percentages are rounded off to the nearest decimal point. ITT Population included all randomized participants in Cohorts A and B regardless of whether the participants received the assigned treatment. Number analyzed is the number of participants with measurable disease at baseline.

End point type	Secondary

End point timeframe:

From randomization up to 27 months for Cohort A and up to 24.4 months for Cohort B

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	167	75	144
Units: percentage of participants				
number (confidence interval 95%)	45.3 (34.58 to 56.45)	46.7 (38.96 to 54.57)	65.3 (53.46 to 75.96)	68.8 (60.50 to 76.21)

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: percentage of participants				
number (confidence interval 95%)	54.9 (44.74 to 64.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: CBR

End point title	Cohort C: CBR[11]

End point description:

CBR was defined as percentage of participants with an objective response (CR or PR), or SD for at least 24 weeks, as determined by the investigator through the use of RECIST v.1.1. CR was defined as the disappearance of all target lesions or any pathological lymph nodes (whether target or non-target) having a reduction in short axis to <10 mm. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Percentages are rounded off to the nearest decimal point. ITT population consisted of all enrolled participants in Cohort C.

End point type	Secondary

End point timeframe:

From enrollment up to 31 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: percentage of participants				
number (confidence interval 95%)	54.9 (44.74 to 64.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort A and B: Change From Baseline in Global Health Status (GHS)/Health-Related Quality of Life (HRQoL) Score Measured by GHS/HRQoL Scale (Questions 29 and 30) of the EORTC QLQ-C30

End point title	Cohort A and B: Change From Baseline in Global Health Status (GHS)/Health-Related Quality of Life (HRQoL) Score Measured by GHS/HRQoL Scale (Questions 29 and 30) of the EORTC QLQ-C30[12]

End point description:

European Organisation for Research&Treatment of Cancer Quality of Life Questionnaire Core 30(EORTC QLQ-C30)=cancer-specific instrument with 30 questions to assess overall QoL. First 28 questions used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much)to evaluate 5 functional scales(physical,role,social,cognitive,emotional),8 symptom scales(diarrhea,fatigue,dyspnea,appetite loss,insomnia,nausea & vomiting,constipation,& pain)&1 item(financial difficulties).Last 2 questions=participant's opinion of overall HQoL,used 7-point scale(1=very poor-7=excellent).Scores were linearly transformed on a scale of 0-100,high score=better GHS/QoL.Negative change from Baseline=deterioration in QoL/functioning & positive values=improvement.PRO-evaluable Population.Number analyzed= number of participants with data available for analyses.'n'=number of participants with data available for analysis at given time point.99999=SD not estimable for a single participant.999=0 participants analysed.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 (cycle length=28 days)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohorts A and B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	160	73	127
Units: score on scale				
arithmetic mean (standard deviation)				
Day 1 Cycle 2 (n= 79, 60, 73, 127)	0.95 (± 20.59)	-0.26 (± 24.58)	4.79 (± 15.83)	-3.61 (± 21.45)
Day 1 Cycle 3 (n= 72, 143, 70, 121)	-0.93 (± 20.53)	0.35 (± 21.73)	1.19 (± 19.62)	-2.13 (± 17.99)
Day 1 Cycle 4 (n= 62, 124, 63, 113)	-4.44 (± 19.42)	-2.42 (± 21.95)	-0.79 (± 21.10)	-1.99 (± 20.75)
Day 1 Cycle 5 (n= 56, 93, 56, 108)	-2.08 (± 16.46)	-2.87 (± 18.61)	-1.19 (± 20.00)	-3.01 (± 18.70)
Day 1 Cycle 6 (n= 48, 77, 53, 101)	-6.94 (± 15.97)	-2.06 (± 21.04)	1.42 (± 19.18)	-3.88 (± 20.67)
Day 1 Cycle 7 (n= 35, 61, 49, 94)	-5.48 (± 12.45)	-3.28 (± 20.93)	0.34 (± 20.34)	-4.17 (± 19.47)
Day 1 Cycle 8 (n= 29, 51, 48, 89)	-6.90 (± 13.56)	0.33 (± 22.11)	0.35 (± 16.84)	-5.99 (± 18.55)
Day 1 Cycle 9 (n= 22, 43, 38, 78)	0.00 (± 10.29)	-3.49 (± 25.28)	1.10 (± 18.80)	-7.37 (± 20.05)
Day 1 Cycle 10 (n= 21, 35, 39, 70)	-2.38 (± 9.91)	-4.52 (± 21.61)	1.28 (± 19.64)	-6.43 (± 18.83)
Day 1 Cycle 11 (n= 17, 28, 35, 65)	-3.43 (± 15.88)	-4.46 (± 21.09)	2.38 (± 22.83)	-5.13 (± 19.30)
Day 1 Cycle 12 (n= 11, 23, 31, 58)	0.76 (± 11.46)	-8.33 (± 19.94)	0.00 (± 22.46)	-4.02 (± 16.32)
Day 1 Cycle 13 (n= 8, 19, 24, 43)	-5.21 (± 10.85)	-8.33 (± 23.57)	-2.43 (± 21.63)	-4.65 (± 18.57)
Day 1 Cycle 14 (n= 7, 14, 22, 38)	-2.38 (± 10.45)	-3.57 (± 19.26)	-0.76 (± 21.81)	-3.29 (± 15.68)
Day 1 Cycle 15 (n= 6, 13, 15, 27)	-9.72 (± 11.08)	-5.77 (± 12.90)	-2.22 (± 18.49)	-0.62 (± 20.14)
Day 1 Cycle 16 (n= 5, 11, 14, 25)	-6.67 (± 13.69)	-8.33 (± 14.91)	-4.7 (± 19.27)	-2.33 (± 16.05)
Day 1 Cycle 17 (n= 4, 11, 12, 21)	-8.33 (± 9.62)	-6.82 (± 13.34)	-7.64 (± 15.27)	-5.95 (± 13.73)
Day 1 Cycle 18 (n= 4, 7, 9, 14)	-8.33 (± 9.62)	-15.48 (± 16.96)	-9.26 (± 19.74)	-6.55 (± 16.07)
Day 1 Cycle 19 (n= 4, 5, 5, 12)	-4.17 (± 8.33)	-20.00 (± 7.45)	-11.67 (± 16.24)	-7.64 (± 23.96)
Day 1 Cycle 20 (n= 2, 3, 4, 10)	-8.33 (± 11.79)	-5.56 (± 9.62)	-16.67 (± 11.79)	-10.00 (± 12.30)
Day 1 Cycle 21 (n= 1, 2, 3, 7)	-16.67 (± 99999)	-16.67 (± 0.00)	-13.89 (± 20.97)	-10.71 (± 13.36)
Day 1 Cycle 22 (n= 0, 0, 3, 7)	-16.67 (± 99999)	-16.67 (± 99999)	-11.11 (± 9.62)	-14.29 (± 15.00)
Day 1 Cycle 23 (n= 1, 1, 3, 7)	-16.67 (± 99999)	-25.00 (± 99999)	-16.67 (± 16.67)	-15.00 (± 18.07)
Day 1 Cycle 24 (n= 0, 0, 3, 7)	-16.67 (± 99999)	-41.67 (± 99999)	-16.67 (± 0.00)	-16.67 (± 11.79)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death from any cause. ITT Population included all randomized participants in Cohorts A and B regardless of whether the participants received the assigned treatment. For Cohort C, the ITT population consisted of all enrolled participants in Cohort C. 9999 indicates that upper limit of 95% CI was not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

From randomization up to death from any cause, up to 45 months for Cohort A, up to 46 months for Cohort B and up to 31 months for Cohort C

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	168	76	146
Units: months				
median (confidence interval 95%)	24.9 (16.9 to 40.4)	24.2 (19.2 to 29.4)	28.4 (20.6 to 37.3)	29.0 (22.4 to 34.8)

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: months				
median (confidence interval 95%)	22.8 (17.8 to 9999)			

Statistical analyses

Statistical analysis title	Placebo vs Ipatasertib
Comparison groups	Cohort B: Placebo + Paclitaxel v Cohort B: Ipatasertib + Paclitaxel
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority[13]
Parameter estimate	Stratified Hazard Ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.37

Notes:

[13] - Stratification variables were: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region, prior therapy with a PI3K or mTOR inhibitor (yes vs. no).

Statistical analysis title	OS
Comparison groups	Cohort A: Placebo + Paclitaxel v Cohort A: Ipatasertib + Paclitaxel
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[14]
Parameter estimate	Stratified Hazard Ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.58

Notes:

[14] - Stratification was done prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region, tumor PIK3CA/AKT1/PTEN alteration status (PIK3CA/AKT1-activating mutations vs. PTEN alterations with no PIK3CA/AKT1-activating mutations).

Secondary: Cohort C: Change From Baseline in GHS/HRQoL Score Measured by GHS/HRQoL Scale (Questions 29 and 30) of the EORTC QLQ-C30

End point title	Cohort C: Change From Baseline in GHS/HRQoL Score Measured by GHS/HRQoL Scale (Questions 29 and 30) of the EORTC QLQ-C30[15]

End point description:

(EORTC QLQ-C30)=cancer-specific instrument with 30 questions to assess overall QoL. First 28 questions used 4-point scale(1=not at all,2=a little,3=quite a bit,4=very much)to evaluate 5 functional scales(physical,role,social,cognitive,emotional),8 symptom scales(diarrhea,fatigue,dyspnea,appetite loss,insomnia,nausea & vomiting,constipation,& pain)&1 item(financial difficulties).Last 2 questions=participant's opinion of overall HQoL,used 7-point scale(1=very poor-7=excellent).Scores were linearly transformed on a scale of 0-100,high score=better GHS/QoL.Negative change from Baseline=deterioration in QoL/functioning & positive values=improvement.PRO-evaluable Population.Number analyzed= number of participants with data available for analyses.'n'=number of participants with data available for analysis at given time point.99999=SD not estimable for a single

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, and 44 (cycle length=28 days)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: score on scale				
arithmetic mean (standard deviation)				
Day 1 Cycle 2 (n= 100)	-0.42 (± 18.02)			

Day 1 Cycle 3 (n=92)	0.18 (± 18.32)			
Day 1 Cycle 4 (n=84)	-4.37 (± 22.83)			
Day 1 Cycle 5 (n=65)	-6.41 (± 20.19)			
Day 1 Cycle 6 (n=61)	-7.10 (± 21.24)			
Day 1 Cycle 7 (n=54)	-5.09 (± 18.02)			
Day 1 Cycle 8 (n=50)	-4.83 (± 21.24)			
Day 1 Cycle 9 (n=37)	-7.66 (± 23.68)			
Day 1 Cycle 10 (n=33)	-7.07 (± 18.76)			
Day 1 Cycle 11 (n=25)	-6.00 (± 19.02)			
Day 1 Cycle 12 (n=23)	-2.90 (± 18.57)			
Day 1 Cycle 13 (n=23)	-1.45 (± 19.08)			
Day 1 Cycle 14 (n=19)	-7.89 (± 21.24)			
Day 1 Cycle 15 (n=18)	-5.09 (± 26.37)			
Day 1 Cycle 16 (n=16)	-11.98 (± 27.55)			
Day 1 Cycle 17 (n=13)	-10.90 (± 32.96)			
Day 1 Cycle 18 (n=13)	-3.85 (± 20.30)			
Day 1 Cycle 19 (n=13)	-3.21 (± 25.35)			
Day 1 Cycle 20 (n=13)	-3.21 (± 24.89)			
Day 1 Cycle 21 (n=13)	-2.56 (± 24.86)			
Day 1 Cycle 22 (n=13)	-12.18 (± 32.92)			
Day 1 Cycle 23 (n=11)	3.03 (± 24.23)			
Day 1 Cycle 24 (n=11)	3.79 (± 24.54)			
Day 1 Cycle 25 (n=9)	-4.63 (± 21.29)			
Day 1 Cycle 26 (n=10)	-0.83 (± 19.82)			
Day 1 Cycle 27 (n=8)	2.08 (± 26.63)			
Day 1 Cycle 28 (n= 6)	1.39 (± 23.81)			
Day 1 Cycle 29 (n= 7)	-1.19 (± 28.64)			
Day 1 Cycle 30 (n= 5)	3.33 (± 24.01)			
Day 1 Cycle 31 (n=3)	22.22 (± 12.73)			
Day 1 Cycle 32 (n=4)	10.42 (± 23.94)			
Day 1 Cycle 33 (n=3)	16.67 (± 22.05)			
Day 1 Cycle 34 (n=3)	16.67 (± 30.05)			
Day 1 Cycle 35 (n=3)	13.89 (± 17.35)			

Day 1 Cycle 36 (n=2)	20.83 (± 29.46)			
Day 1 Cycle 37 (n=2)	16.67 (± 23.57)			
Day 1 Cycle 38 (n=2)	16.67 (± 23.57)			
Day 1 Cycle 39 (n=2)	25.00 (± 35.36)			
Day 1 Cycle 40 (n=1)	33.33 (± 99999)			
Day 1 Cycle 41 (n=1)	50.00 (± 99999)			
Day 1 Cycle 42 (n=1)	41.67 (± 99999)			
Day 1 Cycle 43 (n=1)	41.67 (± 99999)			
Day 1 Cycle 44 (n=1)	50.00 (± 99999)			

Statistical analyses

No statistical analyses for this end point

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 administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. AEs were reported based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. Safety Evaluable Population included all participants who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Up to 58.9 months for Cohort A, up to 59.9 months for Cohort B and up to 45.5 months for Cohort C

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	166	75	145
Units: participants	84	162	74	144

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			

Subject group type	Reporting group			
Number of subjects analysed	102			
Units: participants	102			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort B: Time to Deterioration in Pain

End point title	Cohort B: Time to Deterioration in Pain[16]

End point description:

Time to deterioration in GHS/HRQoL was defined as the time from randomization to first observed ≥ 11-point increase from Baseline in pain scale score (Question 9 and 19) in EORTC QLQ-C30 linearly transformed GHS/HRQoL scale score and was planned to be assessed only in cohort with HR+/HER2 - breast cancer participants (Cohort B). Questions 9 and 19 , that assessed pain, used 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). The scores were linearly transformed on a scale of 0 to 100, with higher scores indicating increased severity in symptoms. ITT Population for Cohort B included as all randomized participants regardless of whether the participants received the assigned treatment. 9999 indicates that data were not estimable not estimable due to insufficient number of participants with events.

End point type	Secondary

End point timeframe:

Baseline up to 24.4 months

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	146		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (11.1 to 9999)		

Statistical analyses

Statistical analysis title	Stratified Analysis
Comparison groups	Cohort B: Placebo + Paclitaxel v Cohort B: Ipatasertib + Paclitaxel
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2162 [17]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	2.22

Notes:

[17] - Stratification variables were: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region, prior therapy with a PI3K or mTOR inhibitor (yes vs. no).

Secondary: Number of Participants with at Least one Adverse Events of Special Interest (AESI)

End point title	Number of Participants with at Least one Adverse Events of Special Interest (AESI)

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. AEs were reported based on the NCI CTCAE, Version 4.0. AESI include cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law. Suspected transmission of an infectious agent by the study drug, Grade >= 3 fasting hyperglycemia, hepatotoxicity, diarrhea, rash, ALT/AST elevations. Grade >= 2 colitis/enterocolitis.

End point type	Secondary

End point timeframe:

Up to 58.9 months for Cohort A, up to 59.9 months for Cohort B and up to 45.5 months for Cohort C

End point values	Cohort A: Placebo + Paclitaxel	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Placebo + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	166	75	141
Units: participants	79	157	73	141

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: participants	101			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts A and B: Plasma Concentration of Ipatasertib

End point title	Cohorts A and B: Plasma Concentration of Ipatasertib[18]

End point description:

PK Evaluable Population included all participants who had at least one evaluable plasma sample. Number analyzed is the number of participants with data available for analyses. 'n' is the number of participants with data available for analysis for the specified time point.

End point type	Secondary

End point timeframe:

Days 1 and 15 of Cycle 1: 1 to 3 hours post dose, and on Day 15 of Cycle 3: 2 to 4 hours post dose (cycle length= 28 days)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohorts A and B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	132		
Units: nanograms per millilitre (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=146, 132, 94)	176 (± 232)	165 (± 326)		
Cycle 1 Day 15 (n=132, 119, 82)	191 (± 184)	211 (± 216)		
Cycle 3 Day 15 (n=110, 102, 62)	165 (± 169)	234 (± 149)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts C: Plasma Concentration of Ipatasertib

End point title	Cohorts C: Plasma Concentration of Ipatasertib[19]

End point description:

PK Evaluable Population included all participants who had at least one evaluable plasma sample. Number analyzed is the number of participants with data available for analyses. 'n' is the number of participants with data available for analysis for the specified time point.

End point type	Secondary

End point timeframe:

Days 1 and 15 of Cycle 1: 1 to 3 hours post dose, and on Day 15 of Cycle 3: 2 to 4 hours post dose (cycle length= 28 days)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	94			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=94)	175 (± 183)			
Cycle 1 Day 15 (n=82)	233 (± 161.6)			
Cycle 3 Day 15 (n=62)	207 (± 197.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohorts A and B: Plasma Concentration of G-037720

End point title	Cohorts A and B: Plasma Concentration of G-037720[20]

End point description:

G-037720 was a metabolite of ipatasertib. PK Evaluable Population included all participants who had at least one evaluable plasma sample. Number analyzed is the number of participants with data available for analyses. 'n' is the number of participants with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Days 1 and 15 of Cycle 1: 1 to 3 hours post dose, and on Day 15 of Cycle 3: 2 to 4 hours post dose (cycle length= 28 days)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohorts A and B. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort A: Ipatasertib + Paclitaxel	Cohort B: Ipatasertib + Paclitaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	123		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=146, 123, 91)	45.6 (± 777)	68.2 (± 405)		
Cycle 1 Day 15 (n=132, 119, 82)	83.9 (± 183)	95.1 (± 211)		
Cycle 3 Day 15 (n=110, 102, 62)	90.8 (± 180)	109 (± 169)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Plasma Concentration of G-037720

End point title	Cohort C: Plasma Concentration of G-037720[21]

End point description:

G-037720 was a metabolite of ipatasertib. PK Evaluable Population included all participants who had at least one evaluable plasma sample. Overall number analyzed is the number of participants with data available for analyses. Number analyzed is the number of participants with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Days 1 and 15 of Cycle 1: 1 to 3 hours post dose, and on Day 15 of Cycle 3: 2 to 4 hours post dose (cycle length= 28 days)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=91)	67.3 (± 222.3)			
Cycle 1 Day 15 (n=82)	96.8 (± 140.7)			
Cycle 3 Day 15 (n=62)	96.5 (± 167.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Serum Concentration of Atezolizumab

End point title	Cohort C: Serum Concentration of Atezolizumab[22]

End point description:

As prespecified in the protocol, this endpoint was applicable only to Cohort C. For Cohort C, PK Evaluable Population included all participants who had at least one evaluable plasma sample in Cohort C. Number analyzed is the number of participants with data available for analysis. 'n' is the number of participants with data available for analysis at the specified time point.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1: 30 minutes post dose, predose on Day 15 of Cycle 1 and predose on Day 1 of Cycles 2, 3, 4, 8, 12 and 16 (cycle length=28 days)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: micrograms per milliliter (ug/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 Cycle 1 (n=84)	309 (± 31.7)			
Day 15 Cycle 1 (n=78)	91.5 (± 23.9)			
Day 1 Cycle 2 (n=92)	130 (± 54.1)			
Day 1 Cycle 3 (n=84)	200 (± 41.1)			
Day 1 Cycle 4 (n=80)	231 (± 52.3)			
Day 1 Cycle 8 (n=46)	327 (± 27.6)			
Day 1 Cycle 12 (n=21)	371 (± 30.5)			
Day 1 Cycle 16 (n=12)	402 (± 42.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: 1-year Event-free OS Rate

End point title	Cohort C: 1-year Event-free OS Rate[23]

End point description:

OS was defined as the time from enrollment to death from any cause. Event-free OS rate was defined as percentage of participants who did not experience any event and survived at 1 year after enrollment. As prespecified in the protocol, this outcome measure was applicable only to Cohort C. ITT Population for Cohort C included all enrolled participants in Cohort C.

End point type	Secondary

End point timeframe:

From randomization up to death from any cause, up to 1 year

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: percentage of participants				
number (confidence interval 95%)	79.38 (71.31 to 87.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: 1-year Event-free PFS Rate

End point title	Cohort C: 1-year Event-free PFS Rate[24]

End point description:

PFS was defined as the time from enrollment to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v.1.1, or death from any cause, whichever occurred first. Event-free PFS rate was defined as percentage of participants who did not experience any event and survived at 1 year after enrollment. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, in addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. Percentages are rounded off to the nearest decimal point. As prespecified in the protocol, this outcome measure was applicable only to Cohort C. ITT Population for Cohort C included all enrolled participants in Cohort C.

End point type	Secondary

End point timeframe:

From enrollment until the occurrence of disease progression or death from any cause, whichever occurred earlier, up to 1 year

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	102			
Units: percentage of participants				
number (confidence interval 95%)	31.17 (21.59 to 40.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort C: Number of Participants with Anti-Drug Antibodies (ADAs) to Atezolizumab

End point title	Cohort C: Number of Participants with Anti-Drug Antibodies (ADAs) to Atezolizumab[25]

End point description:

The numbers of ADA-positive participants after drug administration were summarized for participants exposed to atezolizumab. As prespecified in the protocol, this endpoint was applicable only to Cohort C. For Cohort C, Safety Evaluable Population included all participants who received any amount of study treatment in Cohort C. Number analyzed is the number of participants with an ADA assay result from at least one post-baseline sample.

End point type	Secondary

End point timeframe:

Up to 45.5 months

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is reporting data for only Cohort C. Hence, statistics for all arms in the baseline period is not reported here.

End point values	Cohort C: Ipatasertib + Atezolizumab + Paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: participants	18			

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Up to 58.9 months for Cohort A, up to 59.9 months for Cohort B and up to 45.5 months for Cohort C

Adverse event reporting additional description:

All-cause Mortality: ITT Population=all randomized participants(Cohorts A & B) & enrolled participants (Cohort C) regardless of whether the participants received the assigned treatment.Serious and Other Adverse Events: Safety Evaluable Population=all participants who received any amount of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	COHORT A Placebo + Paclitaxel

Reporting group description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle and placebo, QD, on Days 1 to 21 of each 28-day cycle up to 58.9 months.

Reporting group title	COHORT A Ipatasertib + Paclitaxel

Reporting group description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, at a dose of 400 mg, administered orally QD, on Days 1 to 21 of each 28-day cycle
up to 58.9 months.

Reporting group title	COHORT C Ipatasertib + Atezolizumab + Paclitaxel

Reporting group description:

Participants with histologically confirmed locally advanced unresectable or metastatic TNBC without PIK3CA/AKT1/PTEN-altered tumors and no prior systemic chemotherapy in the advanced disease setting received paclitaxel chemotherapy 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle, ipatasertib at a dose of 400 mg, administered orally QD, on Days 1 to 21 of each 28-day cycle, and atezolizumab 840 mg, IV, on Days 1 and 15 of each 28-day cycle up to 45.5 months.

Reporting group title	COHORT B Ipatasertib + Paclitaxel

Reporting group description:

Participants with histologically confirmed HR+/HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle and ipatasertib, at a dose of 400 mg, administered orally QD, on Days 1 to 21 of each 28-day cycle up to 59.9 months.

Reporting group title	COHORT B Placebo + Paclitaxel

Reporting group description:

Participants with histologically confirmed HR+ /HER2- adenocarcinoma of the breast with PIK3CA/AKT1/PTEN alteration and no prior systemic chemotherapy in the advanced disease setting and who were candidates for taxane monotherapy received paclitaxel chemotherapy, 80 mg/m^2, IV, on Days 1, 8, and 15 of each 28-day cycle and placebo, orally QD, on Days 1 to 21 of each 28-day cycle up to 59.9 months.

Serious adverse events	COHORT A Placebo + Paclitaxel	COHORT A Ipatasertib + Paclitaxel	COHORT C Ipatasertib + Atezolizumab + Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 87 (22.99%)	34 / 166 (20.48%)	29 / 102 (28.43%)
number of deaths (all causes)	41	91	50
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour fistulisation			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected neoplasm			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Tumour necrosis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schwannoma			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Gastric cancer			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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			
Fatigue			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extravasation			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Pyrexia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	4 / 102 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyperthermia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Immune-mediated lung disease			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 87 (0.00%)	3 / 166 (1.81%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	1 / 1
Dyspnoea			
subjects affected / exposed	1 / 87 (1.15%)	1 / 166 (0.60%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 87 (2.30%)	1 / 166 (0.60%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Respiratory distress			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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

Pneumothorax			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Pneumonitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Alanine aminotransferase increased			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Injury, poisoning and procedural complications			
Procedural pain			

subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Femur fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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 laceration			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Road traffic accident			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Spinal fracture			
subjects affected / exposed	1 / 87 (1.15%)	1 / 166 (0.60%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Myocarditis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			

subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Atrial fibrillation			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Cardiac arrest			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Dystonia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 166 (0.60%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 87 (0.00%)	3 / 166 (1.81%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	3 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Leukopenia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Anaemia			
subjects affected / exposed	1 / 87 (1.15%)	1 / 166 (0.60%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Eye disorders			
Macular oedema			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Epiretinal membrane			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Eyelid oedema			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Glaucoma			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 87 (0.00%)	2 / 166 (1.20%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Large intestine perforation			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Abdominal hernia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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 / 87 (0.00%)	2 / 166 (1.20%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 87 (0.00%)	6 / 166 (3.61%)	4 / 102 (3.92%)
occurrences causally related to treatment / all	0 / 0	8 / 8	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Enterocolitis			

subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Cholecystitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema multiforme			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Hydronephrosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
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 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc compression			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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

Gastroenteritis norovirus			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 87 (4.60%)	2 / 166 (1.20%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	2 / 4	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Wound infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess jaw			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Gastroenteritis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected COVID-19			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Viral infection			

subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (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
COVID-19			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysematous cystitis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
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	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Sepsis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Influenza			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Urinary tract infection			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	3 / 102 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			

subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Peritonitis			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Diabetic ketoacidosis			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	0 / 102 (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
Hyperglycaemia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 166 (0.60%)	0 / 102 (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
Tumour lysis syndrome			
subjects affected / exposed	1 / 87 (1.15%)	0 / 166 (0.00%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	2 / 102 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	COHORT B Ipatasertib + Paclitaxel	COHORT B Placebo + Paclitaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 145 (20.69%)	11 / 75 (14.67%)	
number of deaths (all causes)	78	44	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour fistulisation			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schwannoma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			

subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

General physical health deterioration			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperthermia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (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	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Immune-mediated lung disease			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory distress			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 145 (1.38%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			

subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocarditis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dystonia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (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			
Neutropenia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	2 / 145 (1.38%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular oedema			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiretinal membrane			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid oedema			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 145 (2.76%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (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 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 145 (0.69%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			

subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (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 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc compression			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 145 (1.38%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			

subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (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	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysematous cystitis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (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 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Influenza			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 145 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (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			
Decreased appetite			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 145 (0.69%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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 A Placebo + Paclitaxel	COHORT A Ipatasertib + Paclitaxel	COHORT C Ipatasertib + Atezolizumab + Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 87 (94.25%)	161 / 166 (96.99%)	101 / 102 (99.02%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 87 (3.45%)	6 / 166 (3.61%)	8 / 102 (7.84%)
occurrences (all)	3	12	9
Flushing			
subjects affected / exposed	1 / 87 (1.15%)	3 / 166 (1.81%)	8 / 102 (7.84%)
occurrences (all)	2	6	8
Lymphoedema			
subjects affected / exposed	0 / 87 (0.00%)	7 / 166 (4.22%)	2 / 102 (1.96%)
occurrences (all)	0	7	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 87 (11.49%)	35 / 166 (21.08%)	19 / 102 (18.63%)
occurrences (all)	12	40	22
Mucosal inflammation			
subjects affected / exposed	2 / 87 (2.30%)	11 / 166 (6.63%)	12 / 102 (11.76%)
occurrences (all)	4	13	12
Oedema			
subjects affected / exposed	2 / 87 (2.30%)	5 / 166 (3.01%)	3 / 102 (2.94%)
occurrences (all)	2	5	3
Pyrexia			

subjects affected / exposed	6 / 87 (6.90%)	16 / 166 (9.64%)	9 / 102 (8.82%)
occurrences (all)	6	17	13
Fatigue			
subjects affected / exposed	15 / 87 (17.24%)	30 / 166 (18.07%)	23 / 102 (22.55%)
occurrences (all)	16	33	35
Oedema peripheral			
subjects affected / exposed	7 / 87 (8.05%)	18 / 166 (10.84%)	7 / 102 (6.86%)
occurrences (all)	7	23	9
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 87 (5.75%)	4 / 166 (2.41%)	1 / 102 (0.98%)
occurrences (all)	5	8	1
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	3 / 87 (3.45%)	9 / 166 (5.42%)	4 / 102 (3.92%)
occurrences (all)	3	11	5
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	3 / 87 (3.45%)	12 / 166 (7.23%)	8 / 102 (7.84%)
occurrences (all)	5	14	10
Dyspnoea			
subjects affected / exposed	7 / 87 (8.05%)	7 / 166 (4.22%)	9 / 102 (8.82%)
occurrences (all)	9	10	11
Oropharyngeal pain			
subjects affected / exposed	0 / 87 (0.00%)	13 / 166 (7.83%)	6 / 102 (5.88%)
occurrences (all)	0	18	8
Cough			
subjects affected / exposed	10 / 87 (11.49%)	14 / 166 (8.43%)	16 / 102 (15.69%)
occurrences (all)	11	15	18
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 87 (5.75%)	10 / 166 (6.02%)	10 / 102 (9.80%)
occurrences (all)	6	11	10
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	6 / 87 (6.90%)	18 / 166 (10.84%)	21 / 102 (20.59%)
occurrences (all)	7	23	39
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 87 (4.60%)	7 / 166 (4.22%)	7 / 102 (6.86%)
occurrences (all)	4	9	10
Neutrophil count decreased			
subjects affected / exposed	10 / 87 (11.49%)	22 / 166 (13.25%)	8 / 102 (7.84%)
occurrences (all)	23	49	33
Weight decreased			
subjects affected / exposed	3 / 87 (3.45%)	12 / 166 (7.23%)	7 / 102 (6.86%)
occurrences (all)	3	13	7
Weight increased			
subjects affected / exposed	1 / 87 (1.15%)	3 / 166 (1.81%)	6 / 102 (5.88%)
occurrences (all)	4	4	6
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 87 (1.15%)	9 / 166 (5.42%)	12 / 102 (11.76%)
occurrences (all)	1	12	20
White blood cell count decreased			
subjects affected / exposed	7 / 87 (8.05%)	11 / 166 (6.63%)	5 / 102 (4.90%)
occurrences (all)	15	28	10
Alanine aminotransferase increased			
subjects affected / exposed	7 / 87 (8.05%)	23 / 166 (13.86%)	25 / 102 (24.51%)
occurrences (all)	16	29	59
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 87 (3.45%)	6 / 166 (3.61%)	6 / 102 (5.88%)
occurrences (all)	8	6	12
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	20 / 87 (22.99%)	39 / 166 (23.49%)	30 / 102 (29.41%)
occurrences (all)	23	49	41
Paraesthesia			
subjects affected / exposed	2 / 87 (2.30%)	8 / 166 (4.82%)	5 / 102 (4.90%)
occurrences (all)	3	11	7
Dysgeusia			

subjects affected / exposed	8 / 87 (9.20%)	10 / 166 (6.02%)	6 / 102 (5.88%)
occurrences (all)	8	11	6
Headache			
subjects affected / exposed	10 / 87 (11.49%)	28 / 166 (16.87%)	21 / 102 (20.59%)
occurrences (all)	19	56	33
Dizziness			
subjects affected / exposed	8 / 87 (9.20%)	6 / 166 (3.61%)	10 / 102 (9.80%)
occurrences (all)	8	8	14
Polyneuropathy			
subjects affected / exposed	7 / 87 (8.05%)	5 / 166 (3.01%)	8 / 102 (7.84%)
occurrences (all)	7	5	8
Peripheral sensory neuropathy			
subjects affected / exposed	19 / 87 (21.84%)	32 / 166 (19.28%)	8 / 102 (7.84%)
occurrences (all)	19	38	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 87 (26.44%)	43 / 166 (25.90%)	34 / 102 (33.33%)
occurrences (all)	34	58	50
Leukopenia			
subjects affected / exposed	4 / 87 (4.60%)	7 / 166 (4.22%)	11 / 102 (10.78%)
occurrences (all)	11	23	49
Neutropenia			
subjects affected / exposed	20 / 87 (22.99%)	28 / 166 (16.87%)	25 / 102 (24.51%)
occurrences (all)	39	92	114
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 87 (1.15%)	9 / 166 (5.42%)	2 / 102 (1.96%)
occurrences (all)	1	11	2
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	6 / 87 (6.90%)	18 / 166 (10.84%)	7 / 102 (6.86%)
occurrences (all)	12	31	8
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 87 (0.00%)	4 / 166 (2.41%)	5 / 102 (4.90%)
occurrences (all)	0	5	5
Constipation			

subjects affected / exposed	31 / 87 (35.63%)	49 / 166 (29.52%)	13 / 102 (12.75%)
occurrences (all)	40	56	20
Nausea			
subjects affected / exposed	22 / 87 (25.29%)	66 / 166 (39.76%)	42 / 102 (41.18%)
occurrences (all)	29	106	65
Dyspepsia			
subjects affected / exposed	4 / 87 (4.60%)	14 / 166 (8.43%)	6 / 102 (5.88%)
occurrences (all)	4	18	7
Vomiting			
subjects affected / exposed	8 / 87 (9.20%)	53 / 166 (31.93%)	28 / 102 (27.45%)
occurrences (all)	10	112	43
Abdominal pain upper			
subjects affected / exposed	8 / 87 (9.20%)	16 / 166 (9.64%)	6 / 102 (5.88%)
occurrences (all)	10	16	6
Abdominal pain			
subjects affected / exposed	5 / 87 (5.75%)	15 / 166 (9.04%)	12 / 102 (11.76%)
occurrences (all)	6	16	13
Diarrhoea			
subjects affected / exposed	28 / 87 (32.18%)	138 / 166 (83.13%)	86 / 102 (84.31%)
occurrences (all)	56	477	324
Flatulence			
subjects affected / exposed	1 / 87 (1.15%)	5 / 166 (3.01%)	3 / 102 (2.94%)
occurrences (all)	1	6	3
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	3 / 87 (3.45%)	0 / 166 (0.00%)	6 / 102 (5.88%)
occurrences (all)	12	0	13
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	4 / 87 (4.60%)	0 / 166 (0.00%)	1 / 102 (0.98%)
occurrences (all)	5	0	1
Alopecia			
subjects affected / exposed	38 / 87 (43.68%)	78 / 166 (46.99%)	42 / 102 (41.18%)
occurrences (all)	39	80	42
Rash			

subjects affected / exposed	11 / 87 (12.64%)	26 / 166 (15.66%)	29 / 102 (28.43%)
occurrences (all)	13	37	40
Nail discolouration			
subjects affected / exposed	4 / 87 (4.60%)	6 / 166 (3.61%)	1 / 102 (0.98%)
occurrences (all)	4	7	1
Rash maculo-papular			
subjects affected / exposed	0 / 87 (0.00%)	5 / 166 (3.01%)	5 / 102 (4.90%)
occurrences (all)	0	6	5
Erythema			
subjects affected / exposed	5 / 87 (5.75%)	3 / 166 (1.81%)	3 / 102 (2.94%)
occurrences (all)	6	3	3
Pruritus			
subjects affected / exposed	7 / 87 (8.05%)	15 / 166 (9.04%)	17 / 102 (16.67%)
occurrences (all)	8	21	24
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 87 (0.00%)	0 / 166 (0.00%)	6 / 102 (5.88%)
occurrences (all)	0	0	6
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	5 / 87 (5.75%)	16 / 166 (9.64%)	10 / 102 (9.80%)
occurrences (all)	5	24	14
Muscle spasms			
subjects affected / exposed	1 / 87 (1.15%)	4 / 166 (2.41%)	5 / 102 (4.90%)
occurrences (all)	1	4	5
Arthralgia			
subjects affected / exposed	12 / 87 (13.79%)	16 / 166 (9.64%)	13 / 102 (12.75%)
occurrences (all)	18	24	19
Pain in extremity			
subjects affected / exposed	4 / 87 (4.60%)	14 / 166 (8.43%)	4 / 102 (3.92%)
occurrences (all)	5	18	5
Back pain			
subjects affected / exposed	9 / 87 (10.34%)	16 / 166 (9.64%)	10 / 102 (9.80%)
occurrences (all)	14	21	11
Bone pain			

subjects affected / exposed	0 / 87 (0.00%)	7 / 166 (4.22%)	2 / 102 (1.96%)
occurrences (all)	0	9	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 87 (2.30%)	12 / 166 (7.23%)	7 / 102 (6.86%)
occurrences (all)	3	16	9
Upper respiratory tract infection			
subjects affected / exposed	3 / 87 (3.45%)	12 / 166 (7.23%)	8 / 102 (7.84%)
occurrences (all)	3	13	10
Nasopharyngitis			
subjects affected / exposed	3 / 87 (3.45%)	11 / 166 (6.63%)	5 / 102 (4.90%)
occurrences (all)	4	16	5
Cystitis			
subjects affected / exposed	3 / 87 (3.45%)	8 / 166 (4.82%)	2 / 102 (1.96%)
occurrences (all)	5	9	2
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	9 / 87 (10.34%)	31 / 166 (18.67%)	22 / 102 (21.57%)
occurrences (all)	16	49	42
Hypokalaemia			
subjects affected / exposed	3 / 87 (3.45%)	5 / 166 (3.01%)	8 / 102 (7.84%)
occurrences (all)	3	6	10
Hypertriglyceridaemia			
subjects affected / exposed	2 / 87 (2.30%)	9 / 166 (5.42%)	4 / 102 (3.92%)
occurrences (all)	2	11	5
Decreased appetite			
subjects affected / exposed	10 / 87 (11.49%)	29 / 166 (17.47%)	14 / 102 (13.73%)
occurrences (all)	10	35	15

Non-serious adverse events	COHORT B Ipatasertib + Paclitaxel	COHORT B Placebo + Paclitaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 145 (97.24%)	72 / 75 (96.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 145 (5.52%)	4 / 75 (5.33%)	
occurrences (all)	8	7	

Flushing			
subjects affected / exposed	4 / 145 (2.76%)	2 / 75 (2.67%)	
occurrences (all)	5	2	
Lymphoedema			
subjects affected / exposed	6 / 145 (4.14%)	5 / 75 (6.67%)	
occurrences (all)	6	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	27 / 145 (18.62%)	13 / 75 (17.33%)	
occurrences (all)	36	17	
Mucosal inflammation			
subjects affected / exposed	8 / 145 (5.52%)	3 / 75 (4.00%)	
occurrences (all)	11	4	
Oedema			
subjects affected / exposed	9 / 145 (6.21%)	4 / 75 (5.33%)	
occurrences (all)	10	4	
Pyrexia			
subjects affected / exposed	23 / 145 (15.86%)	4 / 75 (5.33%)	
occurrences (all)	30	5	
Fatigue			
subjects affected / exposed	29 / 145 (20.00%)	19 / 75 (25.33%)	
occurrences (all)	36	30	
Oedema peripheral			
subjects affected / exposed	21 / 145 (14.48%)	14 / 75 (18.67%)	
occurrences (all)	28	19	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	3 / 145 (2.07%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	15 / 145 (10.34%)	4 / 75 (5.33%)	
occurrences (all)	17	4	
Dyspnoea			
subjects affected / exposed	10 / 145 (6.90%)	2 / 75 (2.67%)	
occurrences (all)	13	2	
Oropharyngeal pain			
subjects affected / exposed	11 / 145 (7.59%)	2 / 75 (2.67%)	
occurrences (all)	15	3	
Cough			
subjects affected / exposed	23 / 145 (15.86%)	6 / 75 (8.00%)	
occurrences (all)	32	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 145 (4.14%)	6 / 75 (8.00%)	
occurrences (all)	7	6	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 145 (8.97%)	10 / 75 (13.33%)	
occurrences (all)	18	16	
Blood lactate dehydrogenase increased			
subjects affected / exposed	5 / 145 (3.45%)	8 / 75 (10.67%)	
occurrences (all)	7	11	
Neutrophil count decreased			
subjects affected / exposed	23 / 145 (15.86%)	18 / 75 (24.00%)	
occurrences (all)	94	65	
Weight decreased			
subjects affected / exposed	7 / 145 (4.83%)	2 / 75 (2.67%)	
occurrences (all)	8	2	
Weight increased			
subjects affected / exposed	0 / 145 (0.00%)	3 / 75 (4.00%)	
occurrences (all)	0	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 145 (2.07%)	7 / 75 (9.33%)	
occurrences (all)	4	9	
White blood cell count decreased			

subjects affected / exposed	10 / 145 (6.90%)	5 / 75 (6.67%)	
occurrences (all)	44	27	
Alanine aminotransferase increased			
subjects affected / exposed	19 / 145 (13.10%)	15 / 75 (20.00%)	
occurrences (all)	27	30	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	6 / 145 (4.14%)	1 / 75 (1.33%)	
occurrences (all)	6	1	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	46 / 145 (31.72%)	12 / 75 (16.00%)	
occurrences (all)	63	15	
Paraesthesia			
subjects affected / exposed	13 / 145 (8.97%)	6 / 75 (8.00%)	
occurrences (all)	14	8	
Dysgeusia			
subjects affected / exposed	11 / 145 (7.59%)	4 / 75 (5.33%)	
occurrences (all)	12	4	
Headache			
subjects affected / exposed	24 / 145 (16.55%)	8 / 75 (10.67%)	
occurrences (all)	37	19	
Dizziness			
subjects affected / exposed	10 / 145 (6.90%)	3 / 75 (4.00%)	
occurrences (all)	12	4	
Polyneuropathy			
subjects affected / exposed	12 / 145 (8.28%)	6 / 75 (8.00%)	
occurrences (all)	13	6	
Peripheral sensory neuropathy			
subjects affected / exposed	23 / 145 (15.86%)	23 / 75 (30.67%)	
occurrences (all)	30	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	45 / 145 (31.03%)	15 / 75 (20.00%)	
occurrences (all)	57	28	
Leukopenia			

subjects affected / exposed	8 / 145 (5.52%)	7 / 75 (9.33%)	
occurrences (all)	18	16	
Neutropenia			
subjects affected / exposed	36 / 145 (24.83%)	18 / 75 (24.00%)	
occurrences (all)	95	58	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 145 (2.76%)	2 / 75 (2.67%)	
occurrences (all)	4	2	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	16 / 145 (11.03%)	6 / 75 (8.00%)	
occurrences (all)	27	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 145 (2.76%)	4 / 75 (5.33%)	
occurrences (all)	5	4	
Constipation			
subjects affected / exposed	42 / 145 (28.97%)	26 / 75 (34.67%)	
occurrences (all)	54	33	
Nausea			
subjects affected / exposed	60 / 145 (41.38%)	17 / 75 (22.67%)	
occurrences (all)	94	28	
Dyspepsia			
subjects affected / exposed	9 / 145 (6.21%)	4 / 75 (5.33%)	
occurrences (all)	11	6	
Vomiting			
subjects affected / exposed	45 / 145 (31.03%)	6 / 75 (8.00%)	
occurrences (all)	67	10	
Abdominal pain upper			
subjects affected / exposed	15 / 145 (10.34%)	5 / 75 (6.67%)	
occurrences (all)	21	7	
Abdominal pain			
subjects affected / exposed	11 / 145 (7.59%)	7 / 75 (9.33%)	
occurrences (all)	17	9	
Diarrhoea			

subjects affected / exposed	125 / 145 (86.21%)	29 / 75 (38.67%)	
occurrences (all)	461	64	
Flatulence			
subjects affected / exposed	7 / 145 (4.83%)	4 / 75 (5.33%)	
occurrences (all)	7	6	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	6 / 145 (4.14%)	4 / 75 (5.33%)	
occurrences (all)	12	38	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 145 (3.45%)	5 / 75 (6.67%)	
occurrences (all)	5	6	
Alopecia			
subjects affected / exposed	75 / 145 (51.72%)	44 / 75 (58.67%)	
occurrences (all)	79	46	
Rash			
subjects affected / exposed	31 / 145 (21.38%)	9 / 75 (12.00%)	
occurrences (all)	55	13	
Nail discolouration			
subjects affected / exposed	9 / 145 (6.21%)	8 / 75 (10.67%)	
occurrences (all)	9	8	
Rash maculo-papular			
subjects affected / exposed	7 / 145 (4.83%)	4 / 75 (5.33%)	
occurrences (all)	7	7	
Erythema			
subjects affected / exposed	5 / 145 (3.45%)	3 / 75 (4.00%)	
occurrences (all)	5	4	
Pruritus			
subjects affected / exposed	15 / 145 (10.34%)	3 / 75 (4.00%)	
occurrences (all)	25	5	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 145 (0.00%)	0 / 75 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	15 / 145 (10.34%)	9 / 75 (12.00%)	
occurrences (all)	17	12	
Muscle spasms			
subjects affected / exposed	3 / 145 (2.07%)	5 / 75 (6.67%)	
occurrences (all)	5	6	
Arthralgia			
subjects affected / exposed	26 / 145 (17.93%)	10 / 75 (13.33%)	
occurrences (all)	40	16	
Pain in extremity			
subjects affected / exposed	13 / 145 (8.97%)	6 / 75 (8.00%)	
occurrences (all)	24	6	
Back pain			
subjects affected / exposed	21 / 145 (14.48%)	7 / 75 (9.33%)	
occurrences (all)	25	8	
Bone pain			
subjects affected / exposed	9 / 145 (6.21%)	4 / 75 (5.33%)	
occurrences (all)	17	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	16 / 145 (11.03%)	4 / 75 (5.33%)	
occurrences (all)	18	7	
Upper respiratory tract infection			
subjects affected / exposed	14 / 145 (9.66%)	6 / 75 (8.00%)	
occurrences (all)	19	7	
Nasopharyngitis			
subjects affected / exposed	19 / 145 (13.10%)	7 / 75 (9.33%)	
occurrences (all)	24	11	
Cystitis			
subjects affected / exposed	7 / 145 (4.83%)	6 / 75 (8.00%)	
occurrences (all)	12	9	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	19 / 145 (13.10%)	10 / 75 (13.33%)	
occurrences (all)	27	39	
Hypokalaemia			

subjects affected / exposed	6 / 145 (4.14%)	2 / 75 (2.67%)	
occurrences (all)	8	2	
Hypertriglyceridaemia			
subjects affected / exposed	7 / 145 (4.83%)	5 / 75 (6.67%)	
occurrences (all)	8	8	
Decreased appetite			
subjects affected / exposed	21 / 145 (14.48%)	7 / 75 (9.33%)	
occurrences (all)	29	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2017	The following changes were made as per amendment 1: Inclusion criteria was updated to clarify that the pathological diagnosis of receptor status at the time of study entry should be based on the most recent (local or central) testing of Estrogen receptor (ER), progesterone receptor (PR), and HER2 status performed on a biopsy of recurrent or metastatic tissue.
16 February 2018	The following changes were made as per amendment 2: Cohort B participants were required to meet at least one of these criteria •Have primary endocrine resistance, defined as a relapse during the first 2 years of adjuvant endocrine treatment. •Have progressed following at least one line of endocrine-based treatment in the advanced BC setting. •Experience visceral crisis.
15 June 2018	Protocol was updated primarily to expand the testing methods that could be used for biomarker eligibility (to allow local/commercial and blood-based testing), with other minor updates to provide clarity and consistency throughout the protocol. To be eligible for this study, all patients were required to have a valid PIK3CA/AKT1/PTEN alteration by either local/commercial or central testing. In previous versions of the protocol, testing was required to be performed centrally at Foundation Medicine, Inc (FMI) prior to randomization; however, because of the availability of local testing, and the potentially extended time required to obtain central testing results, the protocol was updated to expand the testing methods that could be used for biomarker eligibility. In summary, the inclusion criterion was expanded to also allow tissue or blood-based results from local/commercial tests (using a Clinical Laboratory Improvement Amendments (CLIA) or equivalently accredited diagnostic laboratory) or centrally tested blood-based FMI assay demonstrating a valid PIK3CA/AKT1/PTEN alteration to qualify patients for enrollment in the study. The newly allowed methods enabled patients with existing test results that show qualifying biomarkers to enroll and be randomized without having to wait for the centralized testing result to be completed. It was anticipated that this would shorten the time to treatment for patients and encourage screening for the study.
16 August 2018	The following changes were made as per amendment 5: Updated Cohort B (participants with HR+/HER2- BC) inclusion and exclusion criteria to ensure that participants enrolled were considered to be those patients most likely to benefit from ipatasertib in combination with paclitaxel. Disease-specific inclusion criteria were modified to specify that all participants with HR+/HER2-BC who were not considered appropriate for endocrine-based treatment must also have met one of the following criteria: • Participants had recurrent disease (locoregional or metastatic) during adjuvant endocrine therapy (i.e., ≤5 years of being on therapy). •If participant had de novo metastatic disease, participant has progressive disease within 6 months of being on first-line endocrine treatment of metastatic disease.
04 October 2018	The following changes were made as per amendment 6: Introduced an additional cohort (Cohort C) with an open-label treatment assignment of ipatasertib + atezolizumab + paclitaxel for approximately 100 participants who initially screen for Cohort A (TNBC) but do not qualify for the study (i.e., lack of PIK3CA/AKT1/PTEN alteration validated by central tumor tissue testing using the FMI clinical trial assay (CTA)). Cohort C was introduced as a high biomarker-negative rate, as well as the changing landscape of clinical trial options for patients with first-line advanced TNBC, made recruitment into Cohort A (biomarker-restricted) study. With the addition of Cohort C, up to approximately 100 participants consenting to the lengthy screening process and associated waiting period for biomarker results would have a study treatment assignment even if they do not meet biomarker eligibility for Cohort A, provided other eligibility requirements were met.

27 March 2019	The following changes were made as per amendment 7: Added 5 more countries and updated AE management guidelines in Cohort C for atezolizumab and for the combination of ipatasertib, atezolizumab, and paclitaxel.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported