Clinical trial results:
A Phase Ib/II Study of GDC-0068 or GDC-0980 with Abiraterone Acetate versus Abiraterone Acetate in Patients with Castration-Resistant Prostate Cancer Previously Treated with Docetaxel-Based Chemotherapy

Summary

EudraCT number	2011-004126-10
Trial protocol	GR CZ ES GB NL FR IT
Global end of trial date	31 August 2022

Results information

Result version number	v2 (current)
This version publication date	02 September 2023
First version publication date	07 December 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GO27983

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01485861
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the Phase Ib portion of the study were as follows: To evaluate the safety and tolerability of ipatasertib (GDC-0068), an Akt inhibitor, administered in combination with abiraterone and of apitolisib (GDC-0980), a phosphatidylinositol 3 kinase [PI3K], and/or mammalian target of rapamycin [mTOR] inhibitor, administered in combination with abiraterone. To identify dose-limiting toxicities, estimate the maximum tolerated dose, and identify a recommended Phase II dose of ipatasertib administered in combination with abiraterone and of apitolisib administered in combination with abiraterone. The primary objective of the Phase II portion of the study was to estimate the efficacy as measured by radiographic progression-free survival of ipatasertib (dosed at either 400 milligrams [mg] or 200 mg daily) + abiraterone and prednisone/prednisolone versus placebo + abiraterone and prednisone/prednisolone.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Czechia: 22
Country: Number of subjects enrolled	France: 34
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Romania: 42
Country: Number of subjects enrolled	United States: 54
Worldwide total number of subjects	298
EEA total number of subjects	220

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)	90
From 65 to 84 years	201
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 55 centers in 10 countries.

Pre-assignment

Screening details:

The study consisted of 3 stages: Phase Ib determined recommended Phase II doses (RP2D) for ipatasertib and apitolisib in combination with abiraterone and prednisone/prednisolone. Phase II compared ipatasertib (400 mg/200 mg daily) versus placebo each combined with abiraterone and prednisone/prednisolone. The third stage included the safety cohort.

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, Subject

Blinding implementation details:

The Phase Ib portion of the study was open-label. In Phase II, participants and investigators were blinded with regard to treatment status (i.e., ipatasertib vs. placebo). The Safety cohort was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase Ib: Ipatasertib 400 mg

Arm description:

Participants received ipatasertib 400 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg twice daily (bid) orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	
Other name	GDC-0068
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib was administered orally once daily beginning on Day 1 of Cycle 1 until disease progression or intolerable toxicity.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/prednisolone was to be taken per local clinical practice/investigator recommendation.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered once a day, at the same time that ipatasertib was taken.

Arm title	Phase Ib: Apitolisib 30 mg

Arm description:

Participants received apitolisib 30 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Apitolisib
Investigational medicinal product code	
Other name	GDC-0980
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Apitolisib was administered daily beginning on Day 1 of Cycle 1 until disease progression or intolerable toxicity.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/prednisolone was to be taken per local clinical practice/investigator recommendation.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered once a day, at the same time that ipatasertib was taken.

Arm title	Phase II: Ipatasertib 400 mg + Abiraterone

Arm description:

Participants received ipatasertib 400 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	
Other name	GDC-0068
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib was administered orally once daily beginning on Day 1 of Cycle 1 until disease progression or intolerable toxicity.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/prednisolone was to be taken per local clinical practice/investigator recommendation.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered once a day, at the same time that ipatasertib was taken.

Arm title	Phase II: Ipatasertib 200 mg + Abiraterone

Arm description:

Participants received ipatasertib 200 mg orally once daily, abiraterone 1000 mg once orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	
Other name	GDC-0068
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib was administered orally once daily beginning on Day 1 of Cycle 1 until disease progression or intolerable toxicity.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/prednisolone was to be taken per local clinical practice/investigator recommendation.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered once a day, at the same time that ipatasertib was taken.

Arm title	Phase II: Placebo + Abiraterone

Arm description:

Participants received placebo (matched to ipatasertib 400 mg or 200) orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo (for Ipatasertib 400 mg or 200 mg) was administered daily beginning on Day 1 of Cycle 1 until disease progression or intolerable toxicity.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/prednisolone was to be taken per local clinical practice/investigator recommendation.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered once a day, at the same time that ipatasertib was taken.

Arm title	Safety Cohort: Ipatasertib 400 mg + Abiraterone

Arm description:

Participants received ipatasertib 400 mg orally once daily and/or prednisone/prednisolone 5 mg orally once daily or bid and/or abiraterone 1000 mg orally once daily according to the following schedule: ipatasertib in the morning during Cycle 1, Days 1-7; ipatasertib in the morning plus prednisone/prednisolone once at night during Cycle 1, Day 8; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) during Cycle 1, Days 9-11; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) and abiraterone in the morning during Cycle 1, Days 12-18; ipatasertib in the evening plus prednisone/prednisolone bid (morning and night) and abiraterone at the same time as ipatasertib during Cycle 1, Days 19-25; Cycle 2 and beyond ipatasertib once daily in the morning or evening, abiraterone at the same time as ipatasertib, and prednisone/prednisolone bid.

Arm type	Experimental
Investigational medicinal product name	Ipatasertib
Investigational medicinal product code	
Other name	GDC-0068
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Ipatasertib was administered orally once daily beginning on Day 1 of Cycle 1 until disease progression or intolerable toxicity.

Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	Zytiga®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Abiraterone was administered once a day, at the same time that ipatasertib was taken starting at Cycle 1, Day 18 and then continuously until disease progression or intolerable toxicity.

Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone/prednisolone was to be taken per local clinical practice/investigator recommendation starting on Cycle 1, Day 8.

Number of subjects in period 1	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg	Phase II: Ipatasertib 400 mg + Abiraterone
Started	14	6	84
Completed	0	0	1
Not completed	14	6	83
Physician decision	1	1	-
Consent withdrawn by subject	4	1	6
Study Ended	-	-	7
Discontinuation of Survival Follow-up	-	-	-
Death	1	-	67
Adverse event	-	4	-
Unspecified	3	-	-
Progression of disease	5	-	1
Lost to follow-up	-	-	2

Number of subjects in period 1	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	Safety Cohort: Ipatasertib 400 mg + Abiraterone
Started	86	83	25
Completed	0	0	0
Not completed	86	83	25
Physician decision	-	-	-
Consent withdrawn by subject	3	4	6
Study Ended	8	6	-
Discontinuation of Survival Follow-up	-	-	2
Death	71	68	2
Adverse event	-	-	1
Unspecified	1	-	5
Progression of disease	-	-	9
Lost to follow-up	3	5	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase Ib: Ipatasertib 400 mg
Reporting group description:	
Participants received ipatasertib 400 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg twice daily (bid) orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase Ib: Apitolisib 30 mg
Reporting group description:	
Participants received apitolisib 30 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase II: Ipatasertib 400 mg + Abiraterone
Reporting group description:	
Participants received ipatasertib 400 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase II: Ipatasertib 200 mg + Abiraterone
Reporting group description:	
Participants received ipatasertib 200 mg orally once daily, abiraterone 1000 mg once orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase II: Placebo + Abiraterone
Reporting group description:	
Participants received placebo (matched to ipatasertib 400 mg or 200) orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Safety Cohort: Ipatasertib 400 mg + Abiraterone
Reporting group description:	
Participants received ipatasertib 400 mg orally once daily and/or prednisone/prednisolone 5 mg orally once daily or bid and/or abiraterone 1000 mg orally once daily according to the following schedule: ipatasertib in the morning during Cycle 1, Days 1-7; ipatasertib in the morning plus prednisone/prednisolone once at night during Cycle 1, Day 8; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) during Cycle 1, Days 9-11; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) and abiraterone in the morning during Cycle 1, Days 12-18; ipatasertib in the evening plus prednisone/prednisolone bid (morning and night) and abiraterone at the same time as ipatasertib during Cycle 1, Days 19-25; Cycle 2 and beyond ipatasertib once daily in the morning or evening, abiraterone at the same time as ipatasertib, and prednisone/prednisolone bid.	

Reporting group values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg	Phase II: Ipatasertib 400 mg + Abiraterone
Number of subjects	14	6	84
Age categorical Units: Subjects			

Age continuous			
Number of participants analysed for this parameter were 14, 6, 84, 86, 83, respectively.			
Units: years			
arithmetic mean	68.1	69.3	66.9
standard deviation	± 9.1	± 9.3	± 8.5

Gender categorical Units: Subjects			
Female	0	0	0
Male	14	6	84

Reporting group values	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	Safety Cohort: Ipatasertib 400 mg + Abiraterone
Number of subjects	86	83	25
Age categorical Units: Subjects			

Age continuous			
Number of participants analysed for this parameter were 14, 6, 84, 86, 83, respectively.			
Units: years			
arithmetic mean	68.8	67.6	73.7
standard deviation	± 7.2	± 7.8	± 8.8
Gender categorical Units: Subjects			
Female	0	0	0
Male	86	83	25

Reporting group values	Total		
Number of subjects	298		
Age categorical Units: Subjects			

Age continuous			
Number of participants analysed for this parameter were 14, 6, 84, 86, 83, respectively.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	0		
Male	298		

End points reporting groups

Reporting group title	Phase Ib: Ipatasertib 400 mg
Reporting group description:	
Participants received ipatasertib 400 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg twice daily (bid) orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase Ib: Apitolisib 30 mg
Reporting group description:	
Participants received apitolisib 30 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase II: Ipatasertib 400 mg + Abiraterone
Reporting group description:	
Participants received ipatasertib 400 mg orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase II: Ipatasertib 200 mg + Abiraterone
Reporting group description:	
Participants received ipatasertib 200 mg orally once daily, abiraterone 1000 mg once orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Phase II: Placebo + Abiraterone
Reporting group description:	
Participants received placebo (matched to ipatasertib 400 mg or 200) orally once daily, abiraterone 1000 mg orally once daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.	
Reporting group title	Safety Cohort: Ipatasertib 400 mg + Abiraterone
Reporting group description:	
Participants received ipatasertib 400 mg orally once daily and/or prednisone/prednisolone 5 mg orally once daily or bid and/or abiraterone 1000 mg orally once daily according to the following schedule: ipatasertib in the morning during Cycle 1, Days 1-7; ipatasertib in the morning plus prednisone/prednisolone once at night during Cycle 1, Day 8; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) during Cycle 1, Days 9-11; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) and abiraterone in the morning during Cycle 1, Days 12-18; ipatasertib in the evening plus prednisone/prednisolone bid (morning and night) and abiraterone at the same time as ipatasertib during Cycle 1, Days 19-25; Cycle 2 and beyond ipatasertib once daily in the morning or evening, abiraterone at the same time as ipatasertib, and prednisone/prednisolone bid.	
Subject analysis set title	Safety Set Ipatasertib 400 mg + Abiraterone
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set for Ipatasertib 400 mg + Abiraterone included all treated participants.	
Subject analysis set title	Safety Set Ipatasertib 200 mg + Abiraterone
Subject analysis set type	Safety analysis
Subject analysis set description:	
There were 2 participants who had been randomized to the Placebo + Abiraterone arm, but received 200 mg ipatasertib for 5 days, and are thus counted in the Ipatasertib 200 mg + Abiraterone for the safety population.	
Subject analysis set title	Safety Set Placebo + Abiraterone
Subject analysis set type	Safety analysis
Subject analysis set description:	
There were 2 participants who had been randomized to the Placebo + Abiraterone arm, but received 200 mg ipatasertib for 5 days, and are thus counted in the Ipatasertib 200 mg + Abiraterone for the safety population.	

Primary: Phase Ib: Percentage of Participants With Dose-Limiting Toxicity (DLTs)

End point title	Phase Ib: Percentage of Participants With Dose-Limiting Toxicity (DLTs)[1][2]

End point description:

DLT: 1 of the following toxicities, at least possibly related to ipatasertib or apitolisib. 1) Grade ≥ 3 non-hematologic, non-hepatic major organ AE; 2) Grade ≥ 3 febrile neutropenia; 3) Grade ≥ 4 neutropenia (absolute neutrophils less than [<] 500 per microliter) lasting greater than (>) 7 days; 4) Grade ≥3 thrombocytopenia associated with acute hemorrhage; 5) Grade ≥4 thrombocytopenia; 6) Grade ≥4 anemia; 7) 1 episode of fasting Grade ≥4 hyperglycemia or 3 episodes of fasting Grade 3 hyperglycemia on separate days within 7 days, as determined by laboratory blood glucose evaluation; 8) Grade ≥3 elevation lasting for > 48 hours for hepatic transaminase or liver-specific alkaline phosphatase or total bilirubin. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0. Safety population: all participants who had received ipatasertib, apitolisib, placebo, or abiraterone treatment on Day 1 of Cycle 1.

End point type	Primary

End point timeframe:

Days 1 to 28 of Cycle 1 (Cycle length = 28 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analyses were planned to be reported.

[2] - 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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	6		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase Ib: Percentage of Participants with Adverse Events (AEs)

End point title	Phase Ib: Percentage of Participants with Adverse Events

End point description:

An Adverse Event (AE) was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Safety Population was defined as all participants who had received ipatasertib, apitolisib, placebo, or abiraterone treatment on Day 1 of Cycle 1.

End point type	Primary

End point timeframe:

Baseline up until 30 days following the last administration of study treatment or until initiation of another anti-cancer therapy, whichever occurs first (up to approximately 10 months).

Notes:

[3] - 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: Only descriptive analyses were planned to be reported.

[4] - 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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	6		
Units: percentage of participants				
number (not applicable)	100.0	100.0		

Statistical analyses

No statistical analyses for this end point

Primary: Phase Ib: Recommended Phase II Dose (RP2D) of Ipatasertib and Apitolisib

End point title	Phase Ib: Recommended Phase II Dose (RP2D) of Ipatasertib and Apitolisib[5][6]

End point description:

RP2D is a dose of a drug which would be used in Phase II stage of the study. RP2D was to be determined based on maximum tolerated dose (MTD) in Phase Ib stage of the study. The highest dose level (in 3+3 escalation scheme) with an acceptable safety profile and with a minimum of 6 participants at which fewer than one-third of participants experienced a DLT was declared the MTD and RP2D. Safety Population was defined as all participants who had received ipatasertib, apitolisib, placebo, or abiraterone treatment on Day 1 of Cycle 1.

End point type	Primary

End point timeframe:

Days 1 to 28 of Cycle 1 (Cycle length = 28 days)

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: Only descriptive analyses were planned to be reported.

[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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	0[7]		
Units: milligrams				
number (not applicable)	400			

Notes:

[7] - Based on safety analysis, further testing of apitolisib arm was discontinued.

Statistical analyses

No statistical analyses for this end point

Primary: Phase II: Radiographic Progression Free Survival (rPFS) - ITT Population

End point title	Phase II: Radiographic Progression Free Survival (rPFS) - ITT Population[8]

End point description:

rPFS: Time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments via CT scan and bone scans, or death on study from any cause, whichever occurred first. Progression was defined as follows: Soft tissue mass (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1): at least 20% increase in sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesions. Bone: ≥ 2 new bone lesions plus 2 additional at confirmation on a second bone scan ≥ 4 weeks later (< 12 weeks after randomization). ≥ 2 new bone lesions consistent with progression, without need for confirmatory bone scan (≥ 12 weeks after randomization). ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation.

End point type	Primary

End point timeframe:

Screening up to radiographic progression or death, whichever occurred first (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	83	
Units: months				
median (confidence interval 90%)	8.18 (6.67 to 10.87)	8.31 (6.44 to 10.48)	6.37 (4.60 to 8.34)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1606
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.56
upper limit	1.04

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo

Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.66
upper limit	1.2

Statistical analysis title	Stratified analysis:Ipatasertib 400 mg v Placebo

Statistical analysis description:

Strata were: prior enzalutamide (Yes vs. No), progression factor (prostate-specific antigen [PSA] only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).

Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1689
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.54
upper limit	1.05

Statistical analysis title	Stratified analysis:Ipatasertib 200 mg v Placebo

Statistical analysis description:

Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).

Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7484
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.69
upper limit	1.28

Primary: Phase II: rPFS in Participants With Institute of Cancer Research (ICR) Phosphatase and Tensin Homolog (PTEN) Loss

End point title	Phase II: rPFS in Participants With Institute of Cancer Research (ICR) Phosphatase and Tensin Homolog (PTEN) Loss[9]

End point description:

rPFS: Time from randomization to the first occurrence of disease progression, as determined by investigator review of tumor assessments via CT scan and bone scans, or death on study from any cause, whichever occurred first. Progression was defined as follows: Soft tissue mass (RECIST 1.1): at least 20% increase in sum of diameters of target lesions compared to smallest sum of diameters on-study and absolute increase of at least 5 mm, progression of existing non-target lesions, or presence of new lesions. Bone: ≥ 2 new bone lesions plus 2 additional at confirmation on 2nd bone scan ≥ 4 weeks later (< 12 weeks after randomization). ≥ 2 new bone lesions consistent with progression, without need for confirmatory bone scan (≥ 12 weeks after randomization). PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss.

End point type	Primary

End point timeframe:

Screening up to radiographic progression or death, whichever occurred first (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	21	
Units: months				
median (confidence interval 90%)	11.53 (6.67 to 13.73)	11.10 (6.34 to 16.36)	4.60 (4.40 to 6.37)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0064
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.22
upper limit	0.7

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Placebo + Abiraterone v Phase II: Ipatasertib 200 mg + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0285
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.25
upper limit	0.83

Secondary: Phase Ib: Maximum Plasma Concentration (Cmax) of Ipatasertib When Co-Administered With Abiraterone

End point title	Phase Ib: Maximum Plasma Concentration (Cmax) of Ipatasertib When Co-Administered With Abiraterone[10]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=14)	269 (± 41.3)			
Cycle 1, Day 15 (n=12)	466 (± 36.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Time to Cmax (tmax) of Ipatasertib When Co-Administered With Abiraterone

End point title	Phase Ib: Time to Cmax (tmax) of Ipatasertib When Co-Administered With Abiraterone[11]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=14)	2.00 (0.97 to 4.05)			
Cycle 1, Day 15 (n=12)	2.02 (1.00 to 6.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Area Under The Concentration-Time Curve From Time 0 to 24 Hours (AUC0-24) of Ipatasertib When Co-Administered With Abiraterone

End point title	Phase Ib: Area Under The Concentration-Time Curve From Time 0 to 24 Hours (AUC0-24) of Ipatasertib When Co-Administered With Abiraterone[12]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL*hours				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=14)	1710 (± 54.7)			
Cycle 1, Day 15 (n=12)	3290 (± 37.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Total Body Clearance (CL/F) of Ipatasertib When Co-Administered With Abiraterone

End point title	Phase Ib: Total Body Clearance (CL/F) of Ipatasertib When Co-Administered With Abiraterone[13]

End point description:

Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose is influenced by the fraction of the dose absorbed. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Numer of participants analyzed=participants with PK data available on Day 15 of Cycle 1.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 15 of Cycle 1 (cycle length = 28 days)

Notes:

[13] - 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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: milliliter per hour (mL/h)				
geometric mean (geometric coefficient of variation)	99600 (± 50.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Accumulation Ratio of Ipatasertib When Co-Administered With Abiraterone

End point title	Phase Ib: Accumulation Ratio of Ipatasertib When Co-Administered With Abiraterone[14]

End point description:

Accumulation Ratio was caculated as AUC0-24 (Cycle 1 Day 15) divided by AUC0-24 (Cycle 1 Day 1). Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data Number of participants analyzed=participants with PK data available on both Day 1 and Day 15 of Cycle 1.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

Notes:

[14] - 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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
geometric mean (geometric coefficient of variation)	1.82 (± 40.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Cmax of G-037720 (Metabolite of Ipatasertib)

End point title	Phase Ib: Cmax of G-037720 (Metabolite of Ipatasertib)[15]

End point description:

G-037220 is N-dealkylated metabolite of ipatasertib and the main metabolite in circulation. Analysis was performed on Pharmacokinetic Analysis Population (only ipatasertib arm) which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=14) Cycle 1, Day 15 (n=12)	117 (± 64.4) 326 (± 42.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: tmax of G-037720 (Metabolite of Ipatasertib)

End point title	Phase Ib: tmax of G-037720 (Metabolite of Ipatasertib)[16]

End point description:

G-037220 is N-dealkylated metabolite of ipatasertib and the main metabolite in circulation. Analysis was performed on Pharmacokinetic Analysis Population (only ipatasertib arm) which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=14) Cycle 1, Day 15 (n=12)	2.00 (1.00 to 4.05) 2.10 (1.00 to 6.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: AUC0-24 of G-037720 (Metabolite of Ipatasertib)

End point title	Phase Ib: AUC0-24 of G-037720 (Metabolite of Ipatasertib)[17]

End point description:

G-037220 is N-dealkylated metabolite of ipatasertib and the main metabolite in circulation. Analysis was performed on Pharmacokinetic Analysis Population (only ipatasertib arm) which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

Notes:

[17] - 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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL*hour				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=14) Cycle 1, Day 15 (n=12)	839 (± 70.3) 2850 (± 71.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Accumulation Ratio of G-037720 (Metabolite of Ipatasertib)

End point title	Phase Ib: Accumulation Ratio of G-037720 (Metabolite of Ipatasertib)[18]

End point description:

G-037220 is N-dealkylated metabolite of ipatasertib and the main metabolite in circulation. Accumulation Ratio was caculated as AUC0-24 (Cycle 1 Day 15) divided by AUC0-24 (Cycle 1 Day 1). Analysis was performed on Pharmacokinetic Analysis Population (only ipatasertib arm) which included all participants who had evaluable PK data. Number of participants analyzed=participants with PK data available on both Day 1 and Day 15 of Cycle 1.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (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: Only the arm treated with ipatasertib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ratio				
geometric mean (geometric coefficient of variation)	2.79 (± 54.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Cmax of Apitolisib When Co-Administered With Abiraterone

End point title	Phase Ib: Cmax of Apitolisib When Co-Administered With Abiraterone[19]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (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: Only the arm treated with apitolisib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Apitolisib 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=6) Cycle 1, Day 15 (n=2)	190 (± 35.2) 193 (± 16.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: tmax of Apitolisib When Co-Administered With Abiraterone

End point title	Phase Ib: tmax of Apitolisib When Co-Administered With Abiraterone[20]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (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: Only the arm treated with apitolisib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Apitolisib 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=6) Cycle 1, Day 15 (n=2)	2.02 (1.00 to 4.10) 2.04 (2.00 to 2.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: tmax of Abiraterone When Co- Administered With Ipatasertib or GDC-0980

End point title	Phase Ib: tmax of Abiraterone When Co- Administered With Ipatasertib or GDC-0980[21]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.Cycle 1, Day 1 (n=14,6)

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	6		
Units: hours				
median (full range (min-max))				
Cycle 1, Day 1 (n=14,6)	2.05 (2.00 to 6.45)	2.01 (1.00 to 4.03)		
Cycle 1, Day 15 (n=12,2)	2.17 (2.00 to 6.00)	3.04 (2.00 to 4.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Cmax of Abiraterone When Co- Administered With Ipatasertib or GDC-0980

End point title	Phase Ib: Cmax of Abiraterone When Co- Administered With Ipatasertib or GDC-0980[22]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=14,6)	151 (± 123.6)	88.2 (± 218)		
Cycle 1, Day 15 (n=12,2)	140 (± 124.4)	52.7 (± 182)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: AUC0-24 of Apitolisib When Co-Administered With Abiraterone

End point title	Phase Ib: AUC0-24 of Apitolisib When Co-Administered With Abiraterone[23]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

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: Only the arm treated with apitolisib in Phase Ib was planned to be included in the analysis.

End point values	Phase Ib: Apitolisib 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: ng/mL*hours				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=6) Cycle 1, Day 15 (n=2)	1600 (± 47.5) 1640 (± 5.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: Plasma Half-Life of Abiraterone When Co- Administered With Ipatasertib or GDC-0980

End point title	Phase Ib: Plasma Half-Life of Abiraterone When Co-Administered With Ipatasertib or GDC-0980[24]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint. 99999 = Geometric Coefficient of Variation could not be estimated as only 1 participant was evaluated.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	5		
Units: hours				
geometric mean (geometric coefficient of variation)				

Cycle 1, Day 1 (n=10,5) Cycle 1, Day 15 (n=6,1)	5.25 (± 13.0) 6.92 (± 23.5)	7.68 (± 26.2) 14.70 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase Ib: AUC0-24 of Abiraterone When Co- Administered With Ipatasertib or GDC-0980

End point title	Phase Ib: AUC0-24 of Abiraterone When Co- Administered With Ipatasertib or GDC-0980[25]

End point description:

Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Here, "n" signifies the number of participants with PK data available for specified timepoint. 99999 = Geometric Coefficient of Variation could not be estimated as only 1 participant was evaluated.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: ng/mL*hr				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=12,6)	749 (± 92.0)	475 (± 203.4)		
Cycle 1, Day 15 (n=6,1)	961 (± 87.2)	220 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Overall Survival - ITT Population

End point title	Phase II: Overall Survival - ITT Population[26]

End point description:

Overall survival was defined as the interval between the date of screening and death due to any cause. Overall survival was estimated using Kaplan Meier method. The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation.

End point type	Secondary

End point timeframe:

Screening up to death (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 8.9 years overall]) (cycle length = 28 days)

Notes:

[26] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	83	
Units: months				
median (confidence interval 95%)	18.27 (16.66 to 24.21)	17.31 (13.83 to 22.41)	18.37 (13.80 to 20.96)	

Statistical analyses

Statistical analysis title	Stratified analysis:Ipatasertib 400 mg v Placebo

Statistical analysis description:

Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).

Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5164
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.27

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.417
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.22

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Placebo + Abiraterone v Phase II: Ipatasertib 200 mg + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6712
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.3

Statistical analysis title	Stratified analysis:Ipatasertib 200 mg v Placebo
Statistical analysis description:	
Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).	
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8955
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.44

Secondary: Phase Ib: Accumulation Ratio of Abiraterone When Co- Administered With Ipatasertib or GDC-0980

End point title	Phase Ib: Accumulation Ratio of Abiraterone When Co-Administered With Ipatasertib or GDC-0980[27]

End point description:

Accumulation Ratio was caculated as AUC0-24 (Cycle 1 Day 15) divided by AUC0-24 (Cycle 1 Day 1). Analysis was performed on Pharmacokinetic Analysis Population which included all participants who had evaluable PK data. Number of participants analyzed=participants with PK data available on both Day 1 and Day 15 of Cycle 1. 99999 = Geometric Coefficient of Variation could not be estimated as only 1 participant was evaluated.

End point type	Secondary

End point timeframe:

Pre-dose (0 hour), 1, 2, 4, 6, 24 hours post dose on Days 1, 15 of Cycle 1 (cycle length = 28 days)

Notes:

[27] - 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: Only Phase Ib arms were planned to be included in the analysis.

End point values	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	1		
Units: ratio				
geometric mean (geometric coefficient of variation)	0.823 (± 70.7)	0.882 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Overall Survival in Participants With ICR IHC PTEN Loss

End point title	Phase II: Overall Survival in Participants With ICR IHC PTEN Loss[28]

End point description:

Overall survival was defined as the interval between the date of randomization and death from any cause. Overall survival was estimated using Kaplan Meier method. PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as “ICR PTEN loss”. Number of participants analyzed=participants with PTEN loss.

End point type	Secondary

End point timeframe:

Screening up to death (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 8.9 years overall]) (cycle length = 28 days)

Notes:

[28] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	21	
Units: months				
median (confidence interval 95%)	17.12 (12.32 to 28.02)	28.45 (13.24 to 33.28)	17.28 (11.30 to 20.96)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0157
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.87

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1472
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.19

Secondary: Phase II: Percentage of Participants With PSA Progression in Participants With ICR PTEN Loss

End point title	Phase II: Percentage of Participants With PSA Progression in Participants With ICR PTEN Loss[29]

End point description:

PSA progression was defined as per Prostate Cancer Working Group 2 criteria. PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL from the baseline value, or a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL from the nadir if PSA decreases from baseline after

treatment, which was confirmed by a second value obtained ≥ 3 weeks later. PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss.

End point type	Secondary

End point timeframe:

Screening up to PSA progression (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[29] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	21	
Units: percentage of participants				
number (not applicable)	72.0	64.0	66.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Percentage of Participants With PSA Progression - ITT Population

End point title	Phase II: Percentage of Participants With PSA Progression - ITT Population[30]

End point description:

PSA progression was defined as per Prostate Cancer Working Group 2 criteria. PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 nanogram per milliliter (ng/mL) from the baseline value, or a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL from the nadir if PSA decreases from baseline after treatment, which was confirmed by a second value obtained ≥ 3 weeks later. The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation.

End point type	Secondary

End point timeframe:

Screening up to PSA progression (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[30] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	83	
Units: percentage of participants				
number (not applicable)	57.1	69.8	72.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Time to PSA Progression - ITT Population

End point title	Phase II: Time to PSA Progression - ITT Population[31]

End point description:

Time to PSA progression: Time from screening to the first occurrence of PSA progression, as determined by investigator. PSA progression was defined as per Prostate Cancer Working Group 2 criteria. PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL from the baseline value, or a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL from the nadir if PSA decreases from baseline after treatment, which was confirmed by a second value obtained ≥ 3 weeks later. The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation.

End point type	Secondary

End point timeframe:

Screening up to PSA progression (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[31] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	83	
Units: months				
median (confidence interval 90%)	5.55 (4.17 to 7.39)	3.78 (2.79 to 5.49)	3.71 (2.79 to 4.67)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0665
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.51
upper limit	0.97

Statistical analysis title	Stratified analysis:Ipatasertib 200 mg v Placebo
Statistical analysis description:	
Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).	
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.789
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	1.31

Statistical analysis title	Stratified analysis:Ipatasertib 400 mg v Placebo
Statistical analysis description:	
Strata were: prior Enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).	
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5
upper limit	0.97

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo

Comparison groups	Phase II: Placebo + Abiraterone v Phase II: Ipatasertib 200 mg + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9319
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.33

Secondary: Phase II: Time to PSA Progression in Participants With ICR PTEN Loss

End point title	Phase II: Time to PSA Progression in Participants With ICR PTEN Loss[32]

End point description:

Time to PSA progression: Time from screening to the first occurrence of PSA progression, as determined by investigator. PSA progression was defined as per Prostate Cancer Working Group 2 criteria. PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL from the baseline value, or a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL from the nadir if PSA decreases from baseline after treatment, which was confirmed by a second value obtained ≥ 3 weeks later. PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss.

End point type	Secondary

End point timeframe:

Screening up to PSA progression (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[32] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	21	
Units: months				
median (confidence interval 90%)	3.71 (2.99 to 8.18)	2.92 (2.07 to 7.39)	2.79 (1.02 to 4.67)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2716
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.35
upper limit	1.22

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2906
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.37
upper limit	1.25

Secondary: Phase II: Percentage of Participants With PSA Response in Participants With ICR PTEN Loss

End point title	Phase II: Percentage of Participants With PSA Response in Participants With ICR PTEN Loss[33]

End point description:

PSA response was defined as a > 50% decrease in PSA from baseline, which was to be confirmed after ≥ 4 weeks by a confirmatory PSA measurement. PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose (assessed at baseline, Day 1 of every cycle [starting from Cycle 2] till 30 days after last dose [up to overall 3.6 years]) (cycle length = 28 days)

Notes:

[33] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	21	
Units: percentage of participants				
number (confidence interval 90%)	40.0 (24.57 to 58.32)	44.0 (26.99 to 61.06)	28.6 (13.24 to 46.41)	

Statistical analyses

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4176
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	11.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.43
upper limit	58.32

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2802
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	15.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.58
upper limit	38.44

Secondary: Phase II: Percentage of Participants With PSA Response - ITT Population

End point title	Phase II: Percentage of Participants With PSA Response - ITT Population[34]

End point description:

PSA response was defined as a > 50% decrease in PSA from baseline, which was to be confirmed after ≥ 4 weeks by a confirmatory PSA measurement. The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation.

End point type	Secondary

End point timeframe:

Baseline up to 30 days after last dose (assessed at baseline, Day 1 of every cycle [starting from Cycle 2] till 30 days after last dose [up to overall 3.6 years]) (cycle length = 28 days)

Notes:

[34] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	83	
Units: percentage of participants				
number (confidence interval 90%)	36.9 (28.11 to 46.40)	33.7 (25.29 to 42.93)	34.9 (26.25 to 43.75)	

Statistical analyses

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8675
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-1.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.24
upper limit	10.8

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7913
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	1.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.25
upper limit	14.18

Secondary: Phase II: Percentage of Participants With Objective Response in Participants With ICR PTEN Loss

End point title	Phase II: Percentage of Participants With Objective Response in Participants With ICR PTEN Loss[35]

End point description:

Objective response was defined as having a CR or PR according to a RECIST 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss and evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Screening up to radiographic progression or death, whichever occurred first (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[35] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	15	7	
Units: percentage of participants				
number (confidence interval 90%)	11.1 (1.16 to 39.09)	26.7 (12.18 to 50.00)	14.3 (1.49 to 50.00)	

Statistical analyses

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8489
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-3.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-30.93
upper limit	24.58

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5186
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	12.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	-16.36
upper limit	41.12

Secondary: Phase II: Percentage of Participants With Objective Response - ITT Population

End point title	Phase II: Percentage of Participants With Objective Response - ITT Population[36]

End point description:

Objective response was defined as having a confirm response (CR) or partial response (PR) according to a RECIST 1.1. CR was defined as disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis. PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum diameters), no progression in non-target lesions, and no new lesions. The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation. Number of participants analysed=participants who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Screening up to radiographic progression or death, whichever occurred first (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[36] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37	39	35	
Units: percentage of participants				
number (confidence interval 90%)	32.4 (20.56 to 46.41)	23.1 (13.69 to 35.63)	22.9 (11.91 to 36.46)	

Statistical analyses

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9821
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.89
upper limit	16.33

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3646
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	9.58
Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.65
upper limit	26.8

Secondary: Phase II: Duration of Tumor Response - ITT Population

End point title	Phase II: Duration of Tumor Response - ITT Population[37]

End point description:

Duration of tumor response: time period from 1st documentation of objective response (CR/PR) (whichever status was recorded first) to date of 1st occurrence of investigator documented disease progression or death. CR: disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis. PR: at least 30% decrease in sum of diameters of target lesions (taking as reference baseline sum diameters), no progression in non-target lesions, and no new lesions. Progression: increase by at least 20% in sum of longest diameters of each target lesion, taking as reference smallest sum of longest diameters or appearance of one or more new lesions. Duration of tumor response was estimated using Kaplan Meier method. Number of participants analysed=participants from ITT population who had achieved an objective response. Here, 99999 reflects that data was not evaluable due to insufficient number of events.

End point type	Secondary

End point timeframe:

Screening up to radiographic progression or death, whichever occurred first (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[37] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9	8	
Units: months				
median (confidence interval 90%)	8.77 (3.75 to 99999)	99999 (6.47 to 99999)	99999 (2.76 to 99999)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Placebo + Abiraterone v Phase II: Ipatasertib 400 mg + Abiraterone
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.678
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.31
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.45
upper limit	3.8

Statistical analysis title	Stratified analysis:Ipatasertib 200 mg v Placebo
Statistical analysis description: Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).	
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4227
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.46
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.36
upper limit	16.59

Statistical analysis title	Stratified analysis:Ipatasertib 400 mg v Placebo
Statistical analysis description: Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).	
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7733
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.17
upper limit	3.5

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8372
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.24
upper limit	3.02

Secondary: Phase II: Duration of Tumor Response in Participants with ICR PTEN Loss

End point title	Phase II: Duration of Tumor Response in Participants with ICR PTEN Loss[38]

End point description:

Time from 1st documentation of objective response (CR/PR) to 1st occurrence of investigator documented disease progression or death. CR: disappearance of all target and non-target lesions and no new lesions, all pathological lymph nodes must have decreased to <10 mm in short axis. PR: at least 30% decrease in sum of diameters of target lesions, no progression in non-target lesions, and no new lesions. Progression: increase by at least 20% in sum of longest diameters of each target lesion, taking as reference smallest sum of longest diameters or appearance of one or more new lesions. Estimated using Kaplan Meier method. PTEN status was assessed by RUO IHC assay. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analysed = participants from PTEN loss population who had achieved an objective response. 0.0000/9999/99999 = not estimable due to low number of events

End point type	Secondary

End point timeframe:

Screening up to radiographic progression or death, whichever occurred first (assessed at screening, after Cycles 3, 5, 7, 9, every three cycles [12 weeks] thereafter up to end of treatment [up to 3.6 years overall]) (cycle length = 28 days)

Notes:

[38] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: months				
median (confidence interval 90%)	8.77 (0.0000 to 99999)	9999 (0.99 to 99999)	9999 (0.0000 to 99999)	

Statistical analyses

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6171
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	999.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	99999

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	2
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3173
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	999.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	99999

Secondary: Phase II: Percentage of Participants With Circulating Tumor Cells (CTC) Reduction Response - ITT Population

End point title	Phase II: Percentage of Participants With Circulating Tumor Cells (CTC) Reduction Response - ITT Population[39]

End point description:

CTC reduction response was defined as participants with a reduction in CTCs of ≥ 30% compared to baseline. The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation. Number of participants analysed=participants with CTC > 0 cells/7.5 milliliters (mL) at baseline.

End point type	Secondary

End point timeframe:

Baseline, on Day 1 of Cycle 2, on Day 1 of Cycle 3, and at the treatment completion visit (up to overall 3.6 years) (cycle length=28 days)

Notes:

[39] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	58	62	63	
Units: percentage of participants				
number (confidence interval 90%)	67.2 (56.44 to 77.37)	71.0 (61.07 to 80.32)	63.5 (52.41 to 73.60)	

Statistical analyses

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6652
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	3.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	-10.47
upper limit	17.97

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3734
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	7.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.29
upper limit	21.24

Secondary: Phase II: Percentage of Participants With CTC Conversion - ITT Population

End point title	Phase II: Percentage of Participants With CTC Conversion - ITT Population[40]

End point description:

CTC conversion was defined as a decline to < 5 cells/7.5 milliliter (mL) post baseline among participants with CTC ≥ 5 cells/7.5 mL at baseline. The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation. Number of participants analysed=participants with CTC ≥ 5 cells/7.5 mL at baseline.

End point type	Secondary

End point timeframe:

Baseline, on Day 1 of Cycle 2, on Day 1 of Cycle 3, and at the treatment completion visit (up to overall 3.6 years) (cycle length=28 days)

Notes:

[40] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41	47	48	
Units: percentage of participants				
number (confidence interval 90%)	43.9 (31.18 to 57.87)	46.8 (34.48 to 59.72)	41.7 (29.59 to 54.55)	

Statistical analyses

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6139
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	5.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.6
upper limit	21.88

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8317
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	2.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.07
upper limit	19.54

Secondary: Phase II: Percentage of Participants With CTC Reduction Response in Participants With ICR PTEN Loss

End point title	Phase II: Percentage of Participants With CTC Reduction Response in Participants With ICR PTEN Loss[41]

End point description:

CTC reduction response was defined as participants with a reduction in CTCs of ≥ 30% compared to baseline. PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss and CTC > 0 cells/7.5 mL at baseline.

End point type	Secondary

End point timeframe:

Baseline, on Day 1 of Cycle 2, on Day 1 of Cycle 3, and at the treatment completion visit (up to overall 3.6 years) (cycle length=28 days)

Notes:

[41] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	17	
Units: percentage of participants				
number (confidence interval 90%)	75.0 (55.80 to 87.42)	75.0 (55.80 to 87.42)	70.6 (50.00 to 85.95)	

Statistical analyses

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7633
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	4.41
Confidence interval	
level	90 %
sides	2-sided
lower limit	-19.76
upper limit	28.58

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7633
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	4.41
Confidence interval	
level	90 %
sides	2-sided
lower limit	-19.76
upper limit	28.58

Secondary: Phase II: Percentage of Participants With Pain Progression in Participants With ICR PTEN Loss

End point title	Phase II: Percentage of Participants With Pain Progression in Participants With ICR PTEN Loss[42]

End point description:

Pain progression was defined as ≥ 2 point-increase from baseline on the modified Brief Pain Inventory – short form (mBPI-sf). The mBPI-sf consists of four questions that assess pain intensity (worst, least, average, right now) and seven items within one question that assess the impact of pain on daily functions (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life). Each item was assessed on 0-10 scale with 0 being no pain to 10 being worst imaginable pain. Total score was the average of individual item (range 0-10). PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss.

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle (cycle length=28 days) up to treatment completion (up to 3.6 years)

Notes:

[42] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	21	
Units: percentage of participants				
number (not applicable)	40.0	28.0	33.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Percentage of Participants With Pain Progression - ITT Population

End point title	Phase II: Percentage of Participants With Pain Progression - ITT Population[43]

End point description:

Pain progression was defined as ≥ 2 point-increase from baseline on the modified Brief Pain Inventory – short form (mBPI-sf). The mBPI-sf consists of four questions that assess pain intensity (worst, least, average, right now) and seven items within one question that assess the impact of pain on daily functions (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life). Each item was assessed on 0-10 scale with 0 being no pain to 10 being worst imaginable pain. Total score was the average of individual item (range 0-10). The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation.

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle (cycle length=28 days) up to treatment completion (up to 3.6 years)

Notes:

[43] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	83	
Units: percentage of participants				
number (not applicable)	33.3	34.9	34.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Percentage of Participants With CTC Conversion in Participants With ICR PTEN Loss

End point title	Phase II: Percentage of Participants With CTC Conversion in Participants With ICR PTEN Loss[44]

End point description:

CTC conversion was defined as a decline to < 5 cells/7.5 milliliter (mL) post baseline among participants with CTC ≥ 5 cells/7.5 mL at baseline. PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as "ICR PTEN loss". Number of participants analyzed=participants with PTEN loss and CTC ≥ 5 cells/7.5 mL at baseline.

End point type	Secondary

End point timeframe:

Baseline, on Day 1 of Cycle 2, on Day 1 of Cycle 3, and at the treatment completion visit (up to overall 3.6 years) (cycle length=28 days)

Notes:

[44] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	18	22	
Units: percentage of participants				
number (confidence interval 90%)	66.7 (39.84 to 84.58)	22.2 (10.60 to 41.88)	31.8 (18.11 to 50.00)	

Statistical analyses

Statistical analysis title	Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4989
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	-9.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	-32.54
upper limit	13.35

Statistical analysis title	Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0505
Method	Chi-squared
Parameter estimate	Difference in response rates
Point estimate	34.85
Confidence interval	
level	90 %
sides	2-sided
lower limit	7.14
upper limit	62.56

Secondary: Phase II: Time to Pain Progression - ITT Population

End point title	Phase II: Time to Pain Progression - ITT Population[45]

End point description:

Time to pain progression was defined as the time from screening till first occurrence of pain progression. Pain progression was defined as ≥ 2 point-increase from baseline on the modified Brief Pain Inventory – short form (mBPI-sf). The mBPI-sf consists of four questions that assess pain intensity (worst, least, average, right now) and seven items within one question that assess the impact of pain on daily functions (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life). Each item was assessed on 0-10 scale with 0 being no pain to 10 being worst imaginable pain. Total score was the average of individual item (range 0-10). The ITT Population was defined as all randomised participants with the participants allocated to the treatment arm according to the randomisation. Here, "99999" reflects that the data was not evaluable because of insufficient number of events.

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle (cycle length=28 days) up to treatment completion (up to 3.6 years)

Notes:

[45] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	86	83	
Units: months				
median (confidence interval 90%)	13.90 (8.61 to 99999)	16.16 (8.54 to 99999)	15.15 (11.07 to 99999)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8483
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.61
upper limit	1.47

Statistical analysis title	Stratified analysis:Ipatasertib 200 mg v Placebo
Statistical analysis description:	
Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).	
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8647
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.67
upper limit	1.63

Statistical analysis title	Stratified analysis:Ipatasertib 400 mg v Placebo
Statistical analysis description:	
Strata were: prior enzalutamide (Yes vs. No), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one).	
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8847
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.66
upper limit	1.65

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.785
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	1.65

Secondary: Phase II: Time to Pain Progression in Participants With ICR PTEN Loss

End point title	Phase II: Time to Pain Progression in Participants With ICR PTEN Loss[46]

End point description:

Time to pain progression was defined as the time from screening till first occurrence of pain progression. Pain progression: ≥ 2 point-increase from baseline on the modified Brief Pain Inventory – short form (mBPI-sf). The mBPI-sf consists of 4questions that assess pain intensity (worst, least, average, right now) and seven items within one question that assess the impact of pain on daily functions (general activity, mood, walking ability, normal work, relations with other people, sleep, enjoyment of life). Each item was assessed on 0-10 scale with 0 being no pain to 10 being worst imaginable pain. Total score was the average of individual item (range 0-10). PTEN status was assessed by RUO IHC assay that was performed at ICR, UK. Samples with 100% of the tumor with no PTEN staining were classified as “ICR PTEN loss”. Number of participants analyzed=participants with PTEN loss. Here, "99999" reflects that the data was not evaluable because of insufficient number of events.

End point type	Secondary

End point timeframe:

Screening, Day 1 of each cycle (cycle length=28 days) up to treatment completion (up to 3.6 years)

Notes:

[46] - 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: Only Phase II arms were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	21	
Units: months				
median (confidence interval 90%)	16.49 (7.59 to 16.49)	99999 (8.28 to 99999)	6.93 (5.65 to 99999)	

Statistical analyses

Statistical analysis title	Unstratified analysis:Ipatasertib 200 mg v Placebo
Comparison groups	Phase II: Ipatasertib 200 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7383
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.35
upper limit	2.02

Statistical analysis title	Unstratified analysis:Ipatasertib 400 mg v Placebo
Comparison groups	Phase II: Ipatasertib 400 mg + Abiraterone v Phase II: Placebo + Abiraterone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8271
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.39
upper limit	2.06

Secondary: Phase II: Percentage of Participants With Adverse Events (AEs)

End point title	Phase II: Percentage of Participants With Adverse Events (AEs)

End point description:

An Adverse Event (AE) was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The Safety Population was defined as all participants who had received ipatasertib, apitolisib, placebo, or abiraterone treatment.

End point type	Secondary

End point timeframe:

Baseline up until 30 days following the last administration of study treatment or until initiation of another anti-cancer therapy, whichever occurred first (up to approximately 8.9 years)

End point values	Safety Set Ipatasertib 400 mg + Abiraterone	Safety Set Ipatasertib 200 mg + Abiraterone	Safety Set Placebo + Abiraterone	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	84	88	81	
Units: percentage of participants				
number (not applicable)	98.8	96.6	93.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: Ipatasertib Plasma Concentrations When Co-Administered With Abiraterone

End point title	Phase II: Ipatasertib Plasma Concentrations When Co-Administered With Abiraterone[47]

End point description:

The Pharmacokinetic (PK) Analysis Population was defined as all participants who had evaluable PK data. Data were only analyzed in ipatasertib treatment arms. Total number analyzed represents all participants with evaluations at one or more time points. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Phase II: Cycle 1, Day 1: 1, 4 hours postdose; Cycle 1, Day 15: predose, 2, 4 hours postdose; Cycle 2, Day 1: predose, 1-4 hours postdose (cycle length = 28 days)

Notes:

[47] - 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: Only the arms treated with ipatasertib in Phase II were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	86		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				

Cycle 1, Day 1: 1 hour postdose (n=43, 47)	101 (± 359.5)	63.4 (± 187.2)		
Cycle 1, Day 1: 4 hours postdose (n=72, 76)	180 (± 103.4)	87.0 (± 71.6)		
Cycle 1, Day 15: predose (n=74, 81)	53.1 (± 97.2)	24.5 (± 61.9)		
Cycle 1, Day 15: 2 hours postdose (n=69, 77)	213 (± 174.3)	140 (± 103.7)		
Cycle 1, Day 15: 4 hours postdose (n=72, 77)	272 (± 137.9)	139 (± 69.3)		
Cycle 2, Day 1: predose (n=73, 82)	46.7 (± 138.6)	25.3 (± 49.8)		
Cycle 2, Day 1: 1-4 hours postdose (n=70, 82)	243 (± 94.4)	145 (± 80.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase II: G-037720 (Metabolite of Ipatasertib) Plasma Concentrations

End point title	Phase II: G-037720 (Metabolite of Ipatasertib) Plasma Concentrations[48]

End point description:

The Pharmacokinetic (PK) Analysis Population was defined as all participants who had evaluable PK data. Data were only analyzed in ipatasertib treatment arms. Total number analyzed represents all participants with evaluations at one or more time points. Here, "n" signifies the number of participants with PK data available for specified timepoint.

End point type	Secondary

End point timeframe:

Phase II: Cycle 1, Day 1: 1, 4 hours postdose; Cycle 1, Day 15: predose, 2, 4 hours postdose; Cycle 2, Day 1: predose, 1-4 hours postdose (cycle length = 28 days)

Notes:

[48] - 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: Only the arms treated with ipatasertib in Phase II were planned to be included in the analysis.

End point values	Phase II: Ipatasertib 400 mg + Abiraterone	Phase II: Ipatasertib 200 mg + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	86		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1: 1 hour postdose (n=35, 40)	34.7 (± 223.1)	13.9 (± 268.9)		
Cycle 1, Day 1: 4 hours postdose (n=69, 75)	101 (± 61.8)	42.9 (± 96.6)		
Cycle 1, Day 15: predose (n=73, 80)	44.1 (± 92.4)	20.4 (± 59.2)		
Cycle 1, Day 15: 2 hours postdose (n=69, 77)	121 (± 159.4)	78.0 (± 93.0)		
Cycle 1, Day 15: 4 hours postdose (n=72, 76)	178 (± 134.0)	101 (± 61.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Baseline up until 30 days following the last administration of study treatment or until initiation of another anti-cancer therapy, whichever occurred first (up to approximately 10.7 years)

Adverse event reporting additional description:

The Safety Population was defined as all participants who had received ipatasertib, apitolisib, placebo, or abiraterone treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1, 25.1

Reporting groups

Reporting group title	Phase Ib: Ipatasertib 400 mg

Reporting group description:

Participants received ipatasertib 400 mg orally daily, abiraterone 1000 mg orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Reporting group title	Phase Ib: Apitolisib 30 mg

Reporting group description:

Participants received apitolisib 30 mg orally daily, abiraterone 1000 mg orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Reporting group title	Phase II: Ipatasertib 400 mg + Abiraterone

Reporting group description:

Participants received ipatasertib 400 mg orally daily, abiraterone 1000 mg orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Reporting group title	Phase II: Ipatasertib 200 mg + Abiraterone

Reporting group description:

Participants received ipatasertib 200 mg orally daily, abiraterone 1000 mg orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Reporting group title	Phase II: Placebo + Abiraterone

Reporting group description:

Participants received placebo (for ipatasertib 400 mg or 200) orally daily, abiraterone 1000 mg orally daily, and prednisone/prednisolone 5 mg bid orally continuously in 28-day treatment cycles until disease progression or intolerable toxicity.

Reporting group title	Safety Cohort: Ipatasertib 400 mg + Abiraterone

Reporting group description:

Participants received ipatasertib 400 mg orally once daily and/or prednisone/prednisolone 5 mg orally once daily or bid and/or abiraterone 1000 mg orally once daily according to the following schedule: ipatasertib in the morning during Cycle 1, Days 1-7; ipatasertib in the morning plus prednisone/prednisolone once at night during Cycle 1, Day 8; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) during Cycle 1, Days 9-11; ipatasertib in the morning plus prednisone/prednisolone bid (morning and night) and abiraterone in the morning during Cycle 1, Days 12-18; ipatasertib in the evening plus prednisone/prednisolone bid (morning and night) and abiraterone at the same time as ipatasertib during Cycle 1, Days 19-25; Cycle 2 and beyond ipatasertib once daily in the morning or evening, abiraterone at the same time as ipatasertib, and prednisone/prednisolone bid.

Serious adverse events	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg	Phase II: Ipatasertib 400 mg + Abiraterone
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)	5 / 6 (83.33%)	43 / 84 (51.19%)
number of deaths (all causes)	1	0	67
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 3
Prostatic adenoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell carcinoma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Aortic aneurysm rupture			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Disease progression			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Death			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Asthenia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Acute pulmonary oedema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haematocrit decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (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
Haemoglobin decreased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (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
Injury, poisoning and procedural complications			
Subdural haematoma			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (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
Skull fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Ulna fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 limb fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Accidental overdose			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Fall			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Rib fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Road traffic accident			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Multiple fractures			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Left ventricular failure			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Ischaemic stroke			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Spinal cord compression			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular encephalopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Cerebral haematoma			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (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
Anaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (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
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Ascites			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 upper			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Haematochezia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Enterocolitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Enteritis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Toxic skin eruption			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 14 (7.14%)	2 / 6 (33.33%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 retention			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder perforation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Ureterolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteolysis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma muscle			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Septic shock			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 cord infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 / 14 (0.00%)	0 / 6 (0.00%)	5 / 84 (5.95%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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
Tuberculosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
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 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 14 (7.14%)	2 / 6 (33.33%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	1 / 1	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (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
Ketoacidosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (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 metabolic decompensation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	Safety Cohort: Ipatasertib 400 mg + Abiraterone
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 88 (47.73%)	18 / 81 (22.22%)	6 / 25 (24.00%)
number of deaths (all causes)	72	67	2
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Prostatic adenoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Small cell carcinoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Aortic aneurysm rupture			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Thrombosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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

Pelvic venous thrombosis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Death			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Asthenia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Pain			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Pyrexia			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (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

Malaise			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Pelvic pain			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (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
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Dyspnoea			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Pneumonitis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Acute pulmonary oedema			

subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haematocrit decreased			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Haemoglobin decreased			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Skull fracture			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Radius fracture			

subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Ulna fracture			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Upper limb fracture			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Accidental overdose			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Fall			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (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
Rib fracture			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Road traffic accident			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block			

subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Atrial fibrillation			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Bradycardia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Cardiac failure			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Left ventricular failure			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Dizziness			

subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Ischaemic stroke			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Nervous system disorder			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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 cord compression			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (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
Syncope			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Vascular encephalopathy			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Cerebral haematoma			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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	2 / 88 (2.27%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Constipation			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Ascites			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Abdominal pain			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (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
Diarrhoea			

subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Dyspepsia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Haematochezia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Enterocolitis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Enteritis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Dysphagia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Nausea			

subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Vomiting			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Faecaloma			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Intestinal obstruction			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Toxic skin eruption			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Calculus urinary			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Haematuria			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Renal failure			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric obstruction			

subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (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
Bladder perforation			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Ureterolithiasis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Ureteric stenosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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			
Back pain			
subjects affected / exposed	2 / 88 (2.27%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Osteolysis			

subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Spinal pain			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Haematoma muscle			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Arthralgia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Pain in extremity			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 88 (5.68%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			

subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Cellulitis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Sepsis			
subjects affected / exposed	3 / 88 (3.41%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Septic shock			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (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
Spinal cord infection			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Urinary tract infection			

subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Tuberculosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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
Hypoglycaemia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (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
Dehydration			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (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
Diabetes mellitus inadequate control			

subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Failure to thrive			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Ketoacidosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (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
Malnutrition			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (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

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

Non-serious adverse events	Phase Ib: Ipatasertib 400 mg	Phase Ib: Apitolisib 30 mg	Phase II: Ipatasertib 400 mg + Abiraterone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)	6 / 6 (100.00%)	82 / 84 (97.62%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	10 / 84 (11.90%)
occurrences (all)	1	1	10
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	11 / 84 (13.10%)
occurrences (all)	1	0	15
Hypotension			

subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	3 / 84 (3.57%)
occurrences (all)	1	1	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 14 (64.29%)	1 / 6 (16.67%)	22 / 84 (26.19%)
occurrences (all)	11	1	36
Asthenia			
subjects affected / exposed	4 / 14 (28.57%)	1 / 6 (16.67%)	23 / 84 (27.38%)
occurrences (all)	4	1	36
Gait disturbance			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Mucosal inflammation			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	3	0	4
Thirst			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	1 / 14 (7.14%)	3 / 6 (50.00%)	12 / 84 (14.29%)
occurrences (all)	1	3	28
Pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	7 / 84 (8.33%)
occurrences (all)	0	1	7
Oedema peripheral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	10 / 84 (11.90%)
occurrences (all)	2	0	13
Oedema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Pelvic pain			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	7 / 84 (8.33%)
occurrences (all)	0	0	8
Respiratory, thoracic and mediastinal disorders			
Dry throat			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	7 / 84 (8.33%)
occurrences (all)	1	0	13
Dysphonia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	0	1	1
Dyspnoea exertional			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences (all)	1	0	1
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	11 / 84 (13.10%)
occurrences (all)	0	1	13
Oropharyngeal pain			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	3 / 84 (3.57%)
occurrences (all)	2	1	3
Wheezing			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	0	1	1
Sinus congestion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	2 / 84 (2.38%)
occurrences (all)	1	1	2
Pleural effusion			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Restlessness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	9 / 84 (10.71%)
occurrences (all)	0	0	11
Depression			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	2	0	3
Anxiety			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	1	0	3
Agitation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	2 / 84 (2.38%)
occurrences (all)	2	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	5 / 84 (5.95%)
occurrences (all)	1	0	8
Blood urine present			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	7 / 84 (8.33%)
occurrences (all)	0	0	7
Weight decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	0	0	6
Blood triglycerides increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 84 (4.76%)
occurrences (all)	0	0	8
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	6 / 84 (7.14%)
occurrences (all)	1	0	8
Dizziness			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	11 / 84 (13.10%)
occurrences (all)	4	0	16
Somnolence			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	1	0	3
Lethargy			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	0	1	1
Hypoaesthesia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	2	0	0
Headache			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	9 / 84 (10.71%)
occurrences (all)	3	0	14
Paraesthesia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	0	0	3
Taste disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Tremor			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	19 / 84 (22.62%)
occurrences (all)	2	1	25
Pancytopenia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	3 / 84 (3.57%)
occurrences (all)	2	1	3
Diarrhoea			
subjects affected / exposed	9 / 14 (64.29%)	4 / 6 (66.67%)	65 / 84 (77.38%)
occurrences (all)	14	6	198
Constipation			
subjects affected / exposed	1 / 14 (7.14%)	2 / 6 (33.33%)	8 / 84 (9.52%)
occurrences (all)	1	2	8
Cheilosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	2 / 84 (2.38%)
occurrences (all)	0	1	3
Abdominal pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	9 / 84 (10.71%)
occurrences (all)	1	0	12
Abdominal pain upper			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	8 / 84 (9.52%)
occurrences (all)	0	0	10
Vomiting			

subjects affected / exposed	9 / 14 (64.29%)	3 / 6 (50.00%)	27 / 84 (32.14%)
occurrences (all)	14	3	42
Tongue discolouration			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Retching			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	2	1	0
Rectal haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Oral disorder			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	6 / 14 (42.86%)	4 / 6 (66.67%)	45 / 84 (53.57%)
occurrences (all)	11	4	74
Eructation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences (all)	1	0	1
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	9 / 84 (10.71%)
occurrences (all)	1	1	9
Flatulence			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	1	0	4
Onycholysis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	1	1	2

Haemorrhage subcutaneous			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	1 / 14 (7.14%)	3 / 6 (50.00%)	10 / 84 (11.90%)
occurrences (all)	1	5	16
Rash maculo-papular			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	4 / 84 (4.76%)
occurrences (all)	3	3	9
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	2 / 84 (2.38%)
occurrences (all)	1	1	4
Renal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	0	1	1
Urinary incontinence			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	1	0	3
Hypertonic bladder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	10 / 84 (11.90%)
occurrences (all)	0	0	16
Dysuria			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	8 / 84 (9.52%)
occurrences (all)	1	0	9
Pollakiuria			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	3 / 84 (3.57%)
occurrences (all)	1	1	3
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	17 / 84 (20.24%)
occurrences (all)	4	1	33
Back pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	18 / 84 (21.43%)
occurrences (all)	1	0	25
Bone pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	12 / 84 (14.29%)
occurrences (all)	1	1	20
Flank pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 84 (2.38%)
occurrences (all)	2	0	2
Muscle spasms			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	0	0	5
Muscular weakness			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	1	1	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	7 / 84 (8.33%)
occurrences (all)	1	0	19
Myalgia			
subjects affected / exposed	4 / 14 (28.57%)	1 / 6 (16.67%)	6 / 84 (7.14%)
occurrences (all)	5	1	8
Neck pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 84 (2.38%)
occurrences (all)	2	0	2
Pain in extremity			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	13 / 84 (15.48%)
occurrences (all)	3	0	15
Pain in jaw			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 84 (3.57%)
occurrences (all)	2	0	4
Infections and infestations			
Fungal urethritis			

subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	14 / 84 (16.67%)
occurrences (all)	3	0	16
Nasopharyngitis			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	5 / 84 (5.95%)
occurrences (all)	2	0	6
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	5 / 84 (5.95%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	6 / 84 (7.14%)
occurrences (all)	1	0	9
Hypertriglyceridaemia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 84 (1.19%)
occurrences (all)	1	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 84 (1.19%)
occurrences (all)	0	1	1
Hyperglycaemia			
subjects affected / exposed	6 / 14 (42.86%)	2 / 6 (33.33%)	19 / 84 (22.62%)
occurrences (all)	7	4	26
Failure to thrive			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Hypovolaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	5 / 14 (35.71%)	1 / 6 (16.67%)	21 / 84 (25.00%)
occurrences (all)	5	1	31
Hypokalaemia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 6 (33.33%)	8 / 84 (9.52%)
occurrences (all)	0	2	20

Dehydration			
subjects affected / exposed	3 / 14 (21.43%)	2 / 6 (33.33%)	3 / 84 (3.57%)
occurrences (all)	3	2	3
Increased appetite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	6 / 84 (7.14%)
occurrences (all)	0	0	6
Hypoglycaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 84 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Phase II: Ipatasertib 200 mg + Abiraterone	Phase II: Placebo + Abiraterone	Safety Cohort: Ipatasertib 400 mg + Abiraterone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 88 (89.77%)	76 / 81 (93.83%)	25 / 25 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	5 / 88 (5.68%)	7 / 81 (8.64%)	0 / 25 (0.00%)
occurrences (all)	5	7	0
Hypertension			
subjects affected / exposed	12 / 88 (13.64%)	9 / 81 (11.11%)	1 / 25 (4.00%)
occurrences (all)	13	12	1
Hypotension			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	25 / 88 (28.41%)	24 / 81 (29.63%)	5 / 25 (20.00%)
occurrences (all)	37	32	7
Asthenia			
subjects affected / exposed	20 / 88 (22.73%)	13 / 81 (16.05%)	2 / 25 (8.00%)
occurrences (all)	24	15	4
Gait disturbance			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	1	1	0

Mucosal inflammation			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Thirst			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	12 / 88 (13.64%)	9 / 81 (11.11%)	4 / 25 (16.00%)
occurrences (all)	16	13	5
Pain			
subjects affected / exposed	9 / 88 (10.23%)	2 / 81 (2.47%)	1 / 25 (4.00%)
occurrences (all)	14	2	1
Oedema peripheral			
subjects affected / exposed	9 / 88 (10.23%)	7 / 81 (8.64%)	0 / 25 (0.00%)
occurrences (all)	11	7	0
Oedema			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Penile pain			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	5 / 88 (5.68%)	0 / 81 (0.00%)	1 / 25 (4.00%)
occurrences (all)	7	0	1
Respiratory, thoracic and mediastinal disorders			
Dry throat			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	6 / 88 (6.82%)	7 / 81 (8.64%)	1 / 25 (4.00%)
occurrences (all)	7	7	1
Dysphonia			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Dyspnoea exertional			

subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	9 / 88 (10.23%)	6 / 81 (7.41%)	3 / 25 (12.00%)
occurrences (all)	10	7	5
Oropharyngeal pain			
subjects affected / exposed	2 / 88 (2.27%)	1 / 81 (1.23%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
Wheezing			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Sinus congestion			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	4 / 88 (4.55%)	2 / 81 (2.47%)	0 / 25 (0.00%)
occurrences (all)	4	4	0
Pleural effusion			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	10 / 88 (11.36%)	5 / 81 (6.17%)	2 / 25 (8.00%)
occurrences (all)	10	5	2
Depression			
subjects affected / exposed	3 / 88 (3.41%)	1 / 81 (1.23%)	1 / 25 (4.00%)
occurrences (all)	3	1	1
Anxiety			
subjects affected / exposed	5 / 88 (5.68%)	3 / 81 (3.70%)	2 / 25 (8.00%)
occurrences (all)	5	3	2
Agitation			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	0	1	0

Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 88 (4.55%)	1 / 81 (1.23%)	3 / 25 (12.00%)
occurrences (all)	5	1	10
Blood urine present			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	4 / 88 (4.55%)	1 / 81 (1.23%)	1 / 25 (4.00%)
occurrences (all)	5	2	1
Weight decreased			
subjects affected / exposed	3 / 88 (3.41%)	1 / 81 (1.23%)	3 / 25 (12.00%)
occurrences (all)	4	1	3
Blood triglycerides increased			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
Alanine aminotransferase increased			
subjects affected / exposed	2 / 88 (2.27%)	1 / 81 (1.23%)	3 / 25 (12.00%)
occurrences (all)	2	1	12
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	2 / 88 (2.27%)	3 / 81 (3.70%)	3 / 25 (12.00%)
occurrences (all)	4	3	3
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 88 (0.00%)	3 / 81 (3.70%)	2 / 25 (8.00%)
occurrences (all)	0	3	2
Dizziness			
subjects affected / exposed	6 / 88 (6.82%)	5 / 81 (6.17%)	1 / 25 (4.00%)
occurrences (all)	8	5	1

Somnolence			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Lethargy			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	9	1	0
Headache			
subjects affected / exposed	5 / 88 (5.68%)	6 / 81 (7.41%)	1 / 25 (4.00%)
occurrences (all)	5	9	1
Paraesthesia			
subjects affected / exposed	5 / 88 (5.68%)	3 / 81 (3.70%)	0 / 25 (0.00%)
occurrences (all)	9	3	0
Taste disorder			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	2 / 25 (8.00%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 88 (20.45%)	8 / 81 (9.88%)	2 / 25 (8.00%)
occurrences (all)	37	13	4
Pancytopenia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 88 (1.14%)	3 / 81 (3.70%)	0 / 25 (0.00%)
occurrences (all)	1	4	0
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 88 (0.00%)	4 / 81 (4.94%)	0 / 25 (0.00%)
occurrences (all)	0	4	0
Diarrhoea			

subjects affected / exposed	42 / 88 (47.73%)	20 / 81 (24.69%)	17 / 25 (68.00%)
occurrences (all)	72	36	63
Constipation			
subjects affected / exposed	18 / 88 (20.45%)	16 / 81 (19.75%)	0 / 25 (0.00%)
occurrences (all)	26	22	0
Cheilosis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Abdominal pain lower			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Abdominal pain			
subjects affected / exposed	10 / 88 (11.36%)	3 / 81 (3.70%)	2 / 25 (8.00%)
occurrences (all)	13	3	2
Abdominal pain upper			
subjects affected / exposed	4 / 88 (4.55%)	5 / 81 (6.17%)	0 / 25 (0.00%)
occurrences (all)	5	7	0
Vomiting			
subjects affected / exposed	24 / 88 (27.27%)	12 / 81 (14.81%)	5 / 25 (20.00%)
occurrences (all)	69	24	12
Tongue discolouration			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Retching			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Oral disorder			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	31 / 88 (35.23%)	21 / 81 (25.93%)	12 / 25 (48.00%)
occurrences (all)	44	30	24
Eructation			

subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	7 / 88 (7.95%)	3 / 81 (3.70%)	3 / 25 (12.00%)
occurrences (all)	8	3	6
Flatulence			
subjects affected / exposed	5 / 88 (5.68%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	5	0	0
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Onycholysis			
subjects affected / exposed	1 / 88 (1.14%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 88 (0.00%)	3 / 81 (3.70%)	0 / 25 (0.00%)
occurrences (all)	0	4	0
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	5 / 88 (5.68%)	3 / 81 (3.70%)	2 / 25 (8.00%)
occurrences (all)	7	3	3
Rash maculo-papular			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	7 / 25 (28.00%)
occurrences (all)	2	1	14
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Renal pain			

subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	2 / 88 (2.27%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Hypertonic bladder			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	6 / 88 (6.82%)	5 / 81 (6.17%)	1 / 25 (4.00%)
occurrences (all)	13	6	1
Dysuria			
subjects affected / exposed	2 / 88 (2.27%)	2 / 81 (2.47%)	2 / 25 (8.00%)
occurrences (all)	4	2	2
Pollakiuria			
subjects affected / exposed	9 / 88 (10.23%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	11	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 88 (19.32%)	21 / 81 (25.93%)	3 / 25 (12.00%)
occurrences (all)	30	27	3
Back pain			
subjects affected / exposed	20 / 88 (22.73%)	20 / 81 (24.69%)	1 / 25 (4.00%)
occurrences (all)	41	28	3
Bone pain			
subjects affected / exposed	12 / 88 (13.64%)	18 / 81 (22.22%)	1 / 25 (4.00%)
occurrences (all)	15	20	1
Flank pain			
subjects affected / exposed	3 / 88 (3.41%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
Muscle spasms			
subjects affected / exposed	6 / 88 (6.82%)	2 / 81 (2.47%)	0 / 25 (0.00%)
occurrences (all)	6	2	0
Muscular weakness			

subjects affected / exposed	7 / 88 (7.95%)	3 / 81 (3.70%)	0 / 25 (0.00%)
occurrences (all)	8	3	0
Musculoskeletal chest pain			
subjects affected / exposed	5 / 88 (5.68%)	7 / 81 (8.64%)	0 / 25 (0.00%)
occurrences (all)	8	10	0
Myalgia			
subjects affected / exposed	3 / 88 (3.41%)	5 / 81 (6.17%)	0 / 25 (0.00%)
occurrences (all)	3	5	0
Neck pain			
subjects affected / exposed	4 / 88 (4.55%)	3 / 81 (3.70%)	1 / 25 (4.00%)
occurrences (all)	4	3	1
Pain in extremity			
subjects affected / exposed	13 / 88 (14.77%)	8 / 81 (9.88%)	4 / 25 (16.00%)
occurrences (all)	24	14	4
Pain in jaw			
subjects affected / exposed	1 / 88 (1.14%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Fungal urethritis			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	7 / 88 (7.95%)	6 / 81 (7.41%)	3 / 25 (12.00%)
occurrences (all)	12	9	3
Nasopharyngitis			
subjects affected / exposed	7 / 88 (7.95%)	3 / 81 (3.70%)	0 / 25 (0.00%)
occurrences (all)	9	3	0
Influenza			
subjects affected / exposed	4 / 88 (4.55%)	3 / 81 (3.70%)	0 / 25 (0.00%)
occurrences (all)	4	3	0
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	4 / 88 (4.55%)	4 / 81 (4.94%)	1 / 25 (4.00%)
occurrences (all)	5	5	1
Hypertriglyceridaemia			

subjects affected / exposed	3 / 88 (3.41%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	4	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	7 / 88 (7.95%)	5 / 81 (6.17%)	8 / 25 (32.00%)
occurrences (all)	12	8	18
Failure to thrive			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Hypovolaemia			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	21 / 88 (23.86%)	12 / 81 (14.81%)	2 / 25 (8.00%)
occurrences (all)	28	13	3
Hypokalaemia			
subjects affected / exposed	6 / 88 (6.82%)	7 / 81 (8.64%)	4 / 25 (16.00%)
occurrences (all)	13	9	7
Dehydration			
subjects affected / exposed	2 / 88 (2.27%)	2 / 81 (2.47%)	2 / 25 (8.00%)
occurrences (all)	2	2	2
Increased appetite			
subjects affected / exposed	0 / 88 (0.00%)	0 / 81 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 88 (1.14%)	2 / 81 (2.47%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Hypoglycaemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 81 (1.23%)	2 / 25 (8.00%)
occurrences (all)	0	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2012	The following major changes were made in Amendment: 1) For Phase Ib, the exclusion criteria were changed: Participants who had received selected prior anti-cancer therapies (cytochrome P 17 inhibitors including abiraterone, inhibtors of Akt, PI3K/mTOR) were allowed. 2) For Phase Ib and II, participants who had received previous therapies with ketoconazole and/or MDV3100 (i.e., enzalutamide) were allowed to enroll. 3) The definition of DLT with respect to liver parameters was modified. 4) The number of sites participating in this study was increased from approximately 50 to approximately 70 sites. 5) Prednisolone was added as an alternative to prednisone. 6) Denosumab was added to the list of allowed concomitant therapies.
29 April 2012	The amendment was released to clarify the process for unblinding of treatment assignment by the investigator through the interactive voice response system/interactive web response system.
11 September 2012	The amendment was released to introduce the following main changes: 1) The study was amended to indicate the recommended dose of ipatasertib (GDC-0068, 400 mg daily) in combination with abiraterone for the Phase II part of the study, on the basis of safety and pharmacokinetic data from the Phase Ib portion. In addition, because of adverse events observed with the combination apitolisib (GDC-0980, 30 mg daily) and abiraterone, further exploration of this combination in the study was discontinued. 2) The design of the Phase II portion of the study was amended accordingly. 3) Updated dose-modification guidelines for the management of hyperglycemia, skin toxicity, gastrointestinal toxicities, and pneumonitis were included.
06 March 2013	The following major changes were made in Amendment: 1) Eligibility criteria were modified to exclude patients with poor performance status (Eastern Cooperative Oncology Group [ECOG] 2). 2) Accordingly, the stratification factors in the Phase II portion of the study were changed: randomization was stratified by prior enzalutamide (yes vs. no), progression factor (PSA only vs. other), and number of prior chemotherapy regimens for metastatic disease (one vs. more than one). 3) Dose modification for prednisone was added. 4) Risk of abiraterone on the fetus was added. 5) Dose reduction of ipatasertib/placebo or apitolisib was added as an option for management of fasting Grade ≥ 3 hyperglycemia if fasting glucose levels recovered to Grade less than or equal to 2 within 3 days upon dose interruption. 6) Cases of potential drug-induced liver injury that included an elevated alanine aminotransferase or aspartate aminotransferase in combination with either an elevated bilirubin or clinical jaundice, and suspected transmission of an infectious agent by the study drug were added as protocol defined events of special interest.
27 November 2013	The disease inclusion criterion was updated to align with the study title and rationale that participants who progressed from docetaxel-based chemotherapy (including docetaxel and cabazitaxel, sharing the same cytotoxic mechanism) should be eligible.
15 September 2017	The amendment was released with the following updates: 1) Facilitate study closure of the Phase Ib portion of the study, while allowing current participants in the Phase II portion of the study to stay on treatment. 2) A section on the Management of Selected Identified and Potential Risks of Ipatasertib was added. 3) Laboratory assessments were streamlined and reduced for ongoing participants. 4) The survival follow-up assessments were removed. 5) The use of the following treatments was removed from the list of prohibited therapies: for apitolisib, proton pump inhibitors (it was recommended that these agents be replaced with an H2-receptor antagonist when feasible), and orally administered H2-receptor antagonists within 10 hours before and 2 hours after apitolisib dose.

24 April 2019	The amendment was released with the following updates: 1) Include a new safety cohort to the study. The purpose of the safety cohort was to use new technology, a continuous glucose monitoring device, to assess the impact of ipatasertib monotherapy, ipatasertib plus prednisone/prednisolone, and ipatasertib plus prednisone/prednisolone plus abiraterone on glucose levels. 2) Compare morning versus evening dosing of ipatasertib with regard to its impact on glucose levels. 3) Explore the potential drug-drug interaction between abiraterone and ipatasertib and/or its metabolite, G-037720.
02 June 2020	The amendment was released with the following updates: 1) Harmonize the inclusion criteria of fasting total serum glucose and HbA1c between the Safety cohort and the Phase II portion of the study. 2) Implement additional changes concerning safety reporting and management of risks as well as further definition of the retinal disorder central subfield thickness.
02 June 2021	The amendment was released to clarify the access to ipatasertib for participants assigned to this treatment after completion of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported