Clinical trial results:
A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial Testing Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone in Adult Male Patients with Asymptomatic or Mildly Symptomatic, Previously Untreated, Metastatic Castrate-Resistant Prostate Cancer

Summary

EudraCT number	2016-004429-17
Trial protocol	NO PT DE DK HU GB AT IE BE ES GR PL FR IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	31 March 2023
First version publication date	31 March 2023

Trial information

Trial identification

Sponsor protocol code	CO39303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03072238
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	Interim
Date of interim/final analysis	16 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety, and pharmacokinetics of ipatasertib plus abiraterone and prednisone/prednisolone compared with placebo plus abiraterone and prednisone/prednisolone in subjects with metastatic castrate-resistant prostate cancer (mCRPC).

Protection of trial subjects:

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

Background therapy:

All subjects who did not undergo orchiectomy were on Gonadotropin-releasing hormone (GnRH) agonists or antagonists. All subjects on the study were on prednisone/prednisolone 5mg BID concomitantly with the study medication.

Evidence for comparator: -

Actual start date of recruitment	30 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 67
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 47
Country: Number of subjects enrolled	Canada: 37
Country: Number of subjects enrolled	China: 18
Country: Number of subjects enrolled	Costa Rica: 25
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Spain: 106
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	Hungary: 44
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Italy: 60
Country: Number of subjects enrolled	Japan: 76
Country: Number of subjects enrolled	Korea, Republic of: 68
Country: Number of subjects enrolled	Mexico: 47
Country: Number of subjects enrolled	Norway: 11

Country: Number of subjects enrolled	Poland: 26
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Russian Federation: 106
Country: Number of subjects enrolled	Thailand: 27
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	United States: 107
Worldwide total number of subjects	1101
EEA total number of subjects	395

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)	287
From 65 to 84 years	786
85 years and over	28

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 181 centers in 26 countries.

Pre-assignment

Screening details:

A total of 1611 subjects were screened, out of which 510 subjects failed screening. A total of 1101 subjects were enrolled at 181 sites.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Abiraterone

Arm description:

Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

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

Dosage and administration details:

Placebo was administered orally once daily (QD).

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 administered orally twice daily (BID) at a dose of 5mg.

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

Dosage and administration details:

Abiraterone was administered orally once daily (QD) at a dose of 1000mg.

Arm title	Ipatasertib + Abiraterone

Arm description:

Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

Arm type	Experimental

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

Dosage and administration details:

Ipatasertib was administered orally once daily (QD) at a dose of 400mg.

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 administered orally twice daily (BID) at a dose of 5mg.

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

Dosage and administration details:

Abiraterone was administered orally once daily (QD) at a dose of 1000mg.

Number of subjects in period 1	Placebo + Abiraterone	Ipatasertib + Abiraterone
Started	554	547
Completed	0	0
Not completed	554	547
Ongoing on study	377	367
Consent withdrawn by subject	30	51
Physician decision	1	3
Death	139	121
Not specified	-	1
Lost to follow-up	7	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Abiraterone
Reporting group description:	
Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.	
Reporting group title	Ipatasertib + Abiraterone
Reporting group description:	
Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.	

Reporting group values	Placebo + Abiraterone	Ipatasertib + Abiraterone	Total
Number of subjects	554	547	1101
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	141	146	287
From 65-84 years	400	386	786
85 years and over	13	15	28
Age Continuous			
Units: years			
arithmetic mean	69.7	69.4	
standard deviation	± 8.2	± 8.0	-
Sex: Female, Male			
Units:			
Female	0	0	0
Male	554	547	1101
Race/Ethnicity, Customized			
Ethnicity			
Units: Subjects			
Hispanic or Latino	65	66	131
Not Hispanic or Latino	469	452	921
Not Stated	20	29	49
Race/Ethnicity, Customized			
Race			
Units: Subjects			
American Indian or Alaska Native	16	15	31
Asian	109	110	219
Black or African American	9	10	19
Native Hawaiian or other Pacific Islander	1	1	2
White	386	376	762

Unknown	33	35	68

End points

End points reporting groups

Reporting group title	Placebo + Abiraterone
Reporting group description:	
Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.	
Reporting group title	Ipatasertib + Abiraterone
Reporting group description:	
Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.	

Primary: Investigator-Assessed Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (PTEN Loss Population)

End point title	Investigator-Assessed Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (PTEN Loss Population)
End point description:	
Radiographic progression-free survival is defined as time from date of randomization to the first occurrence of documented disease progression, as assessed by the investigator with use of the Prostate Cancer Working Group 3 (PCWG3) criteria or death from any cause, whichever occurs first. Disease progression for soft tissue is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 mm in the sum of diameters of target lesions; progression of non target lesions; the appearance of one or more new lesions. Disease progression for bone lesions is defined as 2 or more new lesions compared to baseline followed by a confirmatory bone scan at least 6 weeks later. rPFS will be analyzed in subjects with phosphatase and tensin homolog (PTEN) - loss tumors (using the Ventana PTEN immunohistochemistry (IHC) assay).	
End point type	Primary
End point timeframe:	
Up to approximately 31 months	

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	260		
Units: Months				
median (confidence interval 95%)	16.5 (13.9 to 17.0)	18.5 (16.3 to 22.1)		

Statistical analyses

Statistical analysis title	(Ipat + Abir) vs (Plac + Abir)
Comparison groups	Placebo + Abiraterone v Ipatasertib + Abiraterone

Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0335
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.98

Primary: Investigator-Assessed Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (Intent-To-Treat (ITT) Population)

End point title	Investigator-Assessed Radiographic Progression-Free Survival (rPFS) per PCWG3 criteria (Intent-To-Treat (ITT) Population)

End point description:

Radiographic progression-free survival is defined as time from date of randomization to the first occurrence of documented disease progression, as assessed by the investigator with use of the Prostate Cancer Working Group 3 (PCWG3) criteria or death from any cause, whichever occurs first. Disease progression for soft tissue is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 mm in the sum of diameters of target lesions; progression of non target lesions; the appearance of one or more new lesions. Disease progression for bone lesions is defined as 2 or more new lesions compared to baseline followed by a confirmatory bone scan at least 6 weeks later. rPFS will be analyzed in the Intent-to-Treat (ITT) population.

End point type	Primary

End point timeframe:

Up to approximately 31 months

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	554	547		
Units: Months				
median (confidence interval 95%)	16.6 (15.6 to 19.1)	19.2 (16.5 to 22.3)		

Statistical analyses

Statistical analysis title	(Ipat + Abir) vs (Plac + Abir)
Comparison groups	Placebo + Abiraterone v Ipatasertib + Abiraterone

Number of subjects included in analysis	1101
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0431
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.99

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[1] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[2] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Function Deterioration

End point title	Time to Function Deterioration

End point description:

Time to function deterioration was defined as the time from the date of randomisation to the date of 10-point or more decrease on either the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) PF (Physical Functioning) or RF (Role Functioning) scale scores (range, 0-100) held for two consecutive assessments, or a 10 point or more score decrease followed by death (any cause) within 28 days, whichever occurs first. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[3] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[4] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Prostate-Specific Antigen (PSA) Progression

End point title	Time to Prostate-Specific Antigen (PSA) Progression

End point description:

Time to PSA progression is defined as the time from the date of randomization to the first occurrence of PSA progression, per the PCWG3 criteria. PSA progression is defined as a PSA increase that is ≥ 25% and ≥ 2 ng/mL above the baseline or the nadir, which is confirmed by a second value ≥ 3 weeks later. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[5] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[6] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initiation of Cytotoxic Chemotherapy

End point title	Time to Initiation of Cytotoxic Chemotherapy

End point description:

Time to initiation of cytotoxic chemotherapy is defined as the time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy (use of antineoplastic agents: docetaxel, cabazitaxel, mitoxantrone, estramustine, cisplatin, carboplatin, cyclophosphamide, doxorubicin, mitomycin, irinotecan, 5-fluorouracil, gemcitabine, or etoposide) for prostate cancer. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[8] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression

End point title	Time to Pain Progression

End point description:

Time to pain progression was defined as the time from randomization to the first occurrence of confirmed clinically meaningful cancer-related pain progression event. Cancer-related pain progression refers to pain onset for subjects who are asymptomatic at baseline or pain worsening for those who are mildly symptomatic at baseline. Pain severity will be graded on a 10-point scale, with 0=no pain and 10=severe pain. Pain severity progression is defined as a ≥ 2-point absolute increase from baseline. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[9] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[10] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator-Assessed rPFS per PCWG3 criteria in Subjects With PTEN-Loss Tumors by Next-Generation Sequencing (NGS)

End point title	Investigator-Assessed rPFS per PCWG3 criteria in Subjects

	With PTEN-Loss Tumors by Next-Generation Sequencing (NGS)

End point description:

Investigator-assessed rPFS is defined as time from date of randomization to the first occurrence of documented disease progression, as assessed by the investigator with use of the Prostate Cancer Working Group 3 (PCWG3) criteria or death from any cause, whichever occurs first and will be analyzed in subjects with PTEN-loss tumors by NGS. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[11] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[12] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

An objective response is defined as a complete response (CR) or partial response (PR) on two consecutive occasions >=4 weeks apart, as determined by the investigator using RECIST v1.1 and PCWG3 criteria, in subjects with measurable disease at baseline. Subjects without a post-baseline tumor assessment will be considered non-responders. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[13] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[14] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: PSA Response Rate

End point title	PSA Response Rate

End point description:

PSA response rate is defined as the percentage of participants achieving a PSA decline ≥50% from baseline. Participants without a post-baseline PSA assessment will be considered non-responders. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	(to)		

Notes:

[15] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[16] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Symptomatic Skeletal Event (SSE)

End point title	Time to Symptomatic Skeletal Event (SSE)

End point description:

Time to SSE is defined as the time interval from the date of randomization to the date of an SSE. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[17]	0[18]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[17] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[18] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Opioid Use

End point title	Time to First Opioid Use

End point description:

Time to first opioid use is defined as the documentation of the first opioid prescription for cancer-related pain followed by the subject's record of opioid intake or availability of an Analgesic Quantification Algorithm (AQA) daily score. Subjects reporting use of opioid for cancer-related pain at baseline will be excluded from the analysis. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[19]	0[20]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[19] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[20] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Ipatasertib at Specified Timepoints

End point title	Plasma Concentrations of Ipatasertib at Specified Timepoints[21]

End point description:

Plasma samples for pharmacokinetic characterization was collected at various timepoints in all subjects. The PK Evaluable population was defined as all participants who received Ipatasertib treatment with evaluable PK samples. Number Analyzed was the number of participants with data available for analyses at the specified timepoint.

End point type	Secondary

End point timeframe:

1-3 hours post-dose (Cycle 1, Day 1; Cycle 1 Day 15 and Cycle 3 Day 1) and pre-dose at steady state (Cycle 1 Day 15, Cycle 3 Day 1, Cycle 6 Day 1) (each 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: Plasma concentrations for ipatasertib are only reported for the arm treated with ipatasertib.

End point values	Ipatasertib + Abiraterone			
Subject group type	Reporting group			
Number of subjects analysed	544			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 Post-dose (n=499)	212 (± 158)			
Cycle 1 Day 15 Pre-dose (n=467)	46.8 (± 160)			
Cycle 1 Day 15 Post-dose (n=413)	247 (± 138)			
Cycle 3 Day 1 Pre-dose (n=407)	35.4 (± 256)			
Cycle 3 Day 1 Post-dose (n=403)	207 (± 156)			
Cycle 6 Day 1 Pre-dose (n=372)	46.1 (± 134)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of Response (DOR) is defined as the time from first occurrence of a documented confirmed objective response until the time of documented disease progression as determined by the investigator using RECIST v1.1 and PCWG3 criteria, or death from any cause, whichever occurs first. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Up to approximately 7 years

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[22]	0[23]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[22] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[23] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An Adverse Event can therefore be any unfavorable and unintended sign (including abnormal laboratory

values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as Adverse Events. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

End point type	Secondary

End point timeframe:

Baseline up until 28 days after the last dose of study drug or initiation of subsequent lines of anti-cancer therapy, whichever occurs first (up to a maximum of 7 years).

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	0[25]		
Units: Percentage of Participants				

Notes:

[24] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

[25] - Data collection is ongoing and results will be disclosed within 1 year from Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Abiraterone at Specified Timepoints

End point title	Plasma Concentrations of Abiraterone at Specified Timepoints

End point description:

Plasma samples for pharmacokinetic characterization was collected at various timepoints in all subjects. The PK Evaluable population was defined as all participants who received Abiraterone treatment with evaluable PK samples. Number Analyzed is the number of participants with data available for analyses at the specified timepoint.

End point type	Secondary

End point timeframe:

Pre-dose at steady state in Cycle 1, Day 15 and Cycle 3 Day 1 (each cycle length= 28 days)

End point values	Placebo + Abiraterone	Ipatasertib + Abiraterone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	537	520		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 15 (n=508; n=470)	11.2 (± 124)	9.40 (± 159)		
Cycle 3 Day 1 (n=492; n=415)	10.4 (± 120)	9.55 (± 159)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up until 28 days after the last dose of study drug or initiation of subsequent lines of anti-cancer therapy, whichever occurs first (up to a maximum of 7 years).

Adverse event reporting additional description:

4 subjects from both treatment arms did not receive any study treatment. 5 subjects randomized to the placebo arm took at least one dose of ipatasertib prior to the Clinical Cut-off Date (CCOD) of 16th March 2020 and so as a result, the safety-evaluable population comprised 1097 subjects (551 in the Ipat + Abi arm and 546 in the Pbo + Abi arm).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Ipatasertib + Abiraterone

Reporting group description:

Subjects received Ipatasertib plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

Reporting group title	Placebo + Abiraterone

Reporting group description:

Subjects received Placebo plus Abiraterone (along with Prednisone/Prednisolone), administered orally in 28-day cycles.

Serious adverse events	Ipatasertib + Abiraterone	Placebo + Abiraterone	
Total subjects affected by serious adverse events			
subjects affected / exposed	218 / 551 (39.56%)	124 / 546 (22.71%)	
number of deaths (all causes)	126	143	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schwannoma			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Artery dissection			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 551 (0.54%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest pain			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse drug reaction			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hernia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	3 / 551 (0.54%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 551 (0.54%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	4 / 551 (0.73%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Disorientation			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 551 (1.27%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	6 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aspartate aminotransferase increased			
subjects affected / exposed	5 / 551 (0.91%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Patella fracture			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 551 (0.36%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Forearm fracture			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fracture displacement			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hip fracture			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypobarism			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis chemical			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skull fracture			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tendon rupture			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 551 (0.54%)	6 / 546 (1.10%)	
occurrences causally related to treatment / all	1 / 3	2 / 6	
deaths causally related to treatment / all	0 / 1	0 / 4	
Acute left ventricular failure			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	5 / 551 (0.91%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 551 (0.54%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	4 / 551 (0.73%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	12 / 551 (2.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	10 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic enteritis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Incarcerated inguinal hernia			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 551 (0.73%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemobilia			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	15 / 551 (2.72%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	16 / 17	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	5 / 551 (0.91%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	3 / 551 (0.54%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	10 / 551 (1.81%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	1 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	3 / 551 (0.54%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dysuria			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	3 / 551 (0.54%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 551 (0.00%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	1 / 551 (0.18%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fasciitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	5 / 551 (0.91%)	6 / 546 (1.10%)	
occurrences causally related to treatment / all	0 / 5	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 551 (0.36%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bullous erysipelas			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 551 (0.18%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cystitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 551 (0.36%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 551 (0.18%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 551 (0.00%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 551 (0.54%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Opportunistic infection			

subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	13 / 551 (2.36%)	7 / 546 (1.28%)	
occurrences causally related to treatment / all	0 / 14	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulpitis dental			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal abscess			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 551 (0.54%)	3 / 546 (0.55%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	4 / 551 (0.73%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Skin infection			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			

subjects affected / exposed	0 / 551 (0.00%)	2 / 546 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 551 (0.36%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	8 / 551 (1.45%)	4 / 546 (0.73%)	
occurrences causally related to treatment / all	0 / 10	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tooth infection			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	11 / 551 (2.00%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	8 / 12	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	23 / 551 (4.17%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	24 / 24	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	3 / 551 (0.54%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 551 (0.36%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 551 (0.18%)	0 / 546 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 551 (0.00%)	1 / 546 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipatasertib + Abiraterone	Placebo + Abiraterone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	541 / 551 (98.19%)	486 / 546 (89.01%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	27 / 551 (4.90%)	36 / 546 (6.59%)	
occurrences (all)	29	39	
Hypertension			

subjects affected / exposed	76 / 551 (13.79%)	82 / 546 (15.02%)	
occurrences (all)	91	113	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	99 / 551 (17.97%)	68 / 546 (12.45%)	
occurrences (all)	135	82	
Pyrexia			
subjects affected / exposed	31 / 551 (5.63%)	20 / 546 (3.66%)	
occurrences (all)	37	22	
Fatigue			
subjects affected / exposed	120 / 551 (21.78%)	94 / 546 (17.22%)	
occurrences (all)	137	114	
Oedema peripheral			
subjects affected / exposed	71 / 551 (12.89%)	48 / 546 (8.79%)	
occurrences (all)	80	56	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	32 / 551 (5.81%)	27 / 546 (4.95%)	
occurrences (all)	33	28	
Cough			
subjects affected / exposed	45 / 551 (8.17%)	45 / 546 (8.24%)	
occurrences (all)	49	48	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	24 / 551 (4.36%)	41 / 546 (7.51%)	
occurrences (all)	25	44	
Investigations			
Weight decreased			
subjects affected / exposed	67 / 551 (12.16%)	16 / 546 (2.93%)	
occurrences (all)	81	18	
Blood creatinine increased			
subjects affected / exposed	34 / 551 (6.17%)	18 / 546 (3.30%)	
occurrences (all)	39	21	
Aspartate aminotransferase increased			

subjects affected / exposed	94 / 551 (17.06%)	59 / 546 (10.81%)	
occurrences (all)	101	72	
Alanine aminotransferase increased			
subjects affected / exposed	110 / 551 (19.96%)	56 / 546 (10.26%)	
occurrences (all)	127	65	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	34 / 551 (6.17%)	45 / 546 (8.24%)	
occurrences (all)	45	59	
Nervous system disorders			
Headache			
subjects affected / exposed	53 / 551 (9.62%)	42 / 546 (7.69%)	
occurrences (all)	60	50	
Dizziness			
subjects affected / exposed	36 / 551 (6.53%)	34 / 546 (6.23%)	
occurrences (all)	41	42	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	107 / 551 (19.42%)	65 / 546 (11.90%)	
occurrences (all)	147	85	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	92 / 551 (16.70%)	47 / 546 (8.61%)	
occurrences (all)	139	57	
Nausea			
subjects affected / exposed	154 / 551 (27.95%)	54 / 546 (9.89%)	
occurrences (all)	193	62	
Dyspepsia			
subjects affected / exposed	35 / 551 (6.35%)	23 / 546 (4.21%)	
occurrences (all)	37	28	
Diarrhoea			
subjects affected / exposed	437 / 551 (79.31%)	123 / 546 (22.53%)	
occurrences (all)	914	164	
Abdominal pain			
subjects affected / exposed	31 / 551 (5.63%)	18 / 546 (3.30%)	
occurrences (all)	37	20	

Constipation			
subjects affected / exposed	44 / 551 (7.99%)	78 / 546 (14.29%)	
occurrences (all)	47	90	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	47 / 551 (8.53%)	6 / 546 (1.10%)	
occurrences (all)	65	7	
Rash			
subjects affected / exposed	141 / 551 (25.59%)	42 / 546 (7.69%)	
occurrences (all)	178	46	
Pruritus			
subjects affected / exposed	45 / 551 (8.17%)	15 / 546 (2.75%)	
occurrences (all)	60	17	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	31 / 551 (5.63%)	27 / 546 (4.95%)	
occurrences (all)	39	32	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	38 / 551 (6.90%)	41 / 546 (7.51%)	
occurrences (all)	44	50	
Musculoskeletal pain			
subjects affected / exposed	30 / 551 (5.44%)	34 / 546 (6.23%)	
occurrences (all)	36	38	
Arthralgia			
subjects affected / exposed	65 / 551 (11.80%)	75 / 546 (13.74%)	
occurrences (all)	84	80	
Back pain			
subjects affected / exposed	81 / 551 (14.70%)	107 / 546 (19.60%)	
occurrences (all)	94	128	
Bone pain			
subjects affected / exposed	39 / 551 (7.08%)	30 / 546 (5.49%)	
occurrences (all)	42	42	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	41 / 551 (7.44%)	39 / 546 (7.14%)	
occurrences (all)	58	48	
Upper respiratory tract infection			
subjects affected / exposed	36 / 551 (6.53%)	49 / 546 (8.97%)	
occurrences (all)	46	58	
Nasopharyngitis			
subjects affected / exposed	44 / 551 (7.99%)	45 / 546 (8.24%)	
occurrences (all)	58	62	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	98 / 551 (17.79%)	51 / 546 (9.34%)	
occurrences (all)	113	64	
Hyperglycaemia			
subjects affected / exposed	211 / 551 (38.29%)	85 / 546 (15.57%)	
occurrences (all)	330	125	
Hypertriglyceridaemia			
subjects affected / exposed	31 / 551 (5.63%)	22 / 546 (4.03%)	
occurrences (all)	35	28	
Hypokalaemia			
subjects affected / exposed	43 / 551 (7.80%)	35 / 546 (6.41%)	
occurrences (all)	62	55	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2017	Following updates were made: [1] Clarification regarding Event reporting for hospitalisation and [2] Update for reviewing and handling protocol deviations.
07 March 2018	Following updates were made: [1] Clarification of glucose level monitoring during all clinic visits; [2] Modification of laboratory assessments for glucose level measurements and [3] Requirement for additional blood glucose level monitoring.
01 June 2018	Following updates were made: [1] Total Study size amended from 850 to 1100 subjects to support key secondary endpoint of overall survival; [2] Modification to plans for China extension cohort; [3] Total length of the study updated; [4] Clarification to Biopsy specimen requirements; [5] Guidance on the recording of opioids consumption for cancer-related pain has been added; [6] Criteria for rescreen has been amended; [7] Guidelines for management of diarrhea and Grade 1 hyperglycaemia updated and [8] Updates to the Statistical Analysis section with a testing algorithm for primary and key secondary endpoints.
19 October 2018	Following updates were made: [1] Addition of language following a Health Authority request to specify criteria for the discontinuation of ipatasertib/placebo and [2] Update to the Secondary Medical Monitor and contact information.
13 February 2019	Following updates were made: [1] Clarification regarding study treatment and concomitant use of CYP3A4 inhibitors or inducers with abiraterone; [2] Clarification on subject withdrawal of consent from the testing of his or her Research Biosample Repository (RBR) samples; [3] Key secondary endpoint of time-to-pain progression has been updated to specify that the initiation of opioid analgesic medication is assessed by the Analgesic Quantification Algorithm (AQA) score and [4] Minor changes have been made to Sections 7, 8 and 9 to reflect updates the Sponsor has made to language regarding data collection and management, ethical considerations and study documentation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported