Clinical trial results:
A Phase 3, Randomized Open-label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants with Metastatic Castration-resistant Prostate Cancer (mCRPC) Who are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment with One Next-generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010)

Summary

EudraCT number	2018-004118-16
Trial protocol	NL GB FR ES IE IT
Global end of trial date	27 January 2024

Results information

Result version number	v1 (current)
This version publication date	02 January 2025
First version publication date	02 January 2025

Trial information

Trial identification

Sponsor protocol code	7339-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03834519
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.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	27 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 March 2022
Global end of trial reached?	Yes
Global end of trial date	27 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess the efficacy and safety of the combination of the polyadenosine 5'-diphosphoribose poly (ADP-ribose) polymerase (PARP) inhibitor olaparib and pembrolizumab in the treatment of participants with mCRPC who have failed to respond to either abiraterone acetate or enzalutamide (but not both) and to chemotherapy. The primary study hypotheses are that the combination of pembrolizumab plus olaparib is superior to abiraterone acetate or enzalutamide with respect to: Overall Survival (OS) and Radiographic progression-free survival (rPFS) per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 as assessed by blinded independent central review (BICR) As of Amendment 06, the Data Monitoring Committee (DMC) is no longer applicable. Participants still on treatment may have the option to continue receiving study intervention or SOC if they are deriving clinical benefit, until discontinuation criteria are met.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 65
Country: Number of subjects enrolled	Austria: 24
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Canada: 42
Country: Number of subjects enrolled	Argentina: 38
Country: Number of subjects enrolled	Chile: 32
Country: Number of subjects enrolled	France: 89
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Ireland: 14
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Japan: 50
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 71
Country: Number of subjects enrolled	Netherlands: 61

Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Taiwan: 31
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	793
EEA total number of subjects	316

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)	188
From 65 to 84 years	600
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants randomized to the next-generation hormonal agent monotherapy (NHA) arm received one of two NHA treatments, per protocol.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + Olaparib

Arm description:

Participants received olaparib 600 mg as two 150 mg oral tablets twice daily (BID) continuously until progression PLUS on Day 1 of each 21-day cycle, pembrolizumab 200 mg by intravenous (IV) infusion for up to 35 cycles (approximately 2 years).

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	MK-7339
Other name	MK-7339 AZD-2281 LYNPARZA®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK-3475
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg

Arm title	Next-generation hormonal agent monotherapy (NHA)

Arm description:

Participants received a single NHA of either abiraterone acetate (participants previously treated with enzalutamide) 1000 mg as two 500 mg or four 250 mg oral tablets once daily (QD) PLUS prednisone or prednisolone 10 mg as one 5 mg tablet BID until progression OR participants received enzalutamide (participants previously treated with abiraterone acetate) 160 mg as four 40 mg oral tablets or capsules OR two 80 mg tablets QD until progression.

Arm type	Active comparator
Investigational medicinal product name	Abiraterone acetate
Investigational medicinal product code	
Other name	ZYTIGA® CB-7630 JNJ-212082
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg	
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	
Other name	XTANDI® MDV-3100 ASP-9785
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 160 mg	
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 10 mg	

Number of subjects in period 1	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)
Started	529	264
Treated	526	256
Completed	0	0
Not completed	529	264
Consent withdrawn by subject	5	8
Physician decision	5	1
Death	368	174
Lost to follow-up	2	1
Sponsor decision	149	80

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + Olaparib
Reporting group description:	
Participants received olaparib 600 mg as two 150 mg oral tablets twice daily (BID) continuously until progression PLUS on Day 1 of each 21-day cycle, pembrolizumab 200 mg by intravenous (IV) infusion for up to 35 cycles (approximately 2 years).	
Reporting group title	Next-generation hormonal agent monotherapy (NHA)
Reporting group description:	
Participants received a single NHA of either abiraterone acetate (participants previously treated with enzalutamide) 1000 mg as two 500 mg or four 250 mg oral tablets once daily (QD) PLUS prednisone or prednisolone 10 mg as one 5 mg tablet BID until progression OR participants received enzalutamide (participants previously treated with abiraterone acetate) 160 mg as four 40 mg oral tablets or capsules OR two 80 mg tablets QD until progression.	

Reporting group values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)	Total
Number of subjects	529	264	793
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)	118	70	188
From 65-84 years	406	194	600
85 years and over	5	0	5
Age Continuous Units: Years			
arithmetic mean	69.9	69.1	
standard deviation	± 7.4	± 7.3	-
Sex: Female, Male Units: Participants			
Female	0	0	0
Male	529	264	793
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	102	59	161
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	1	4	5
White	419	199	618
More than one race	1	0	1
Unknown or Not Reported	4	1	5
Ethnicity (NIH/OMB)			

Units: Subjects			
Hispanic or Latino	71	32	103
Not Hispanic or Latino	441	219	660
Unknown or Not Reported	17	13	30
Measurable Response Evaluation Criteria in Solid Tumors Version 1.1 Disease Status at Baseline			
Measurable disease at baseline is defined as having disease that is Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)-measurable lesions per blinded independent central review (BICR).			
Units: Subjects			
RECIST Measurable: Yes	244	119	363
RECIST Measurable: No	285	145	430
Prior Use of NHA Treatment			
Prior use of NHA treatment was defined as prior treatment with Abiraterone only, Enzalutamide only, or Abiraterone and Enzalutamide.			
Units: Subjects			
Abiraterone only	289	143	432
Enzalutamide only	240	120	360
Abiraterone and Enzalutamide	0	1	1

End points

End points reporting groups

Reporting group title	Pembrolizumab + Olaparib
Reporting group description:	
Participants received olaparib 600 mg as two 150 mg oral tablets twice daily (BID) continuously until progression PLUS on Day 1 of each 21-day cycle, pembrolizumab 200 mg by intravenous (IV) infusion for up to 35 cycles (approximately 2 years).	
Reporting group title	Next-generation hormonal agent monotherapy (NHA)
Reporting group description:	
Participants received a single NHA of either abiraterone acetate (participants previously treated with enzalutamide) 1000 mg as two 500 mg or four 250 mg oral tablets once daily (QD) PLUS prednisone or prednisolone 10 mg as one 5 mg tablet BID until progression OR participants received enzalutamide (participants previously treated with abiraterone acetate) 160 mg as four 40 mg oral tablets or capsules OR two 80 mg tablets QD until progression.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall survival (OS) is defined as the time from randomization to death due to any cause. The nonparametric Kaplan-Meier method was used to estimate the survival curves. The analysis population included all randomized participants.	
End point type	Primary
End point timeframe:	
Up to ~31 months	

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	264		
Units: Months				
median (confidence interval 95%)	15.8 (14.6 to 17.0)	14.6 (12.6 to 17.3)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA
Statistical analysis description:	
Treatment difference in OS assessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.	
Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent monotherapy (NHA)

Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2616
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.14

Primary: Radiographic Progression-Free Survival (rPFS)

End point title	Radiographic Progression-Free Survival (rPFS)

End point description:

rPFS is defined as the time from randomization to the first documented progressive disease (PD) per PCWG-modified RECIST 1.1 based on BICR or death due to any cause, whichever occurred first. Per PCWG-modified RECIST 1.1, PD is defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. The appearance of one or more new lesions or ≥2 new bone lesions was also considered PD. PCWG-modified RECIST is similar to RECIST 1.1 with the exception that a confirmation assessment of PD (>4 weeks after the initial PD) is required for participants who remain on treatment following a documented PD per RECIST 1.1 and PCWG rules include new bone lesions. The rPFS per PCWG-modified RECIST as assessed by BICR for all participants is presented. The nonparametric Kaplan-Meier method was used to estimate the survival curves. The analysis population included all randomized participants.

End point type	Primary

End point timeframe:

Up to ~26 months

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	264		
Units: Months				
median (confidence interval 95%)	4.4 (4.2 to 6.0)	4.2 (4.0 to 6.1)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA

Statistical analysis description:

Treatment difference in rPFS aassessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.

Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent

	monotherapy (NHA)
Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5544
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.25

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants with Complete Response (CR: disappearance of all target lesions per RECIST 1.1 and no evidence of disease (NED) bone scan) or Partial Response (PR: at least a 30% decrease in the sum of diameters of target lesions per RECIST 1.1 and Non-PD, non-evaluable (NE), or NED bone scan or CR with non-PD or NE bone scan.) The analysis population included all randomized participants who had measurable disease at baseline. The percentage of participants who experienced CR or PR as assessed by BICR is presented.

End point type	Secondary

End point timeframe:

Up to ~31 months

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	119		
Units: Percentage of Participants				
number (confidence interval 95%)	16.8 (12.3 to 22.1)	5.9 (2.4 to 11.7)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA

Statistical analysis description:

Treatment difference in ORR assessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.

Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent monotherapy (NHA)

Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in percentage
Point estimate	10.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	17.1

Secondary: Time to Initiation of the First Subsequent Anticancer Therapy (TFST)

End point title	Time to Initiation of the First Subsequent Anticancer Therapy (TFST)

End point description:

TFST is the time from randomization to initiation of the first subsequent anticancer therapy defined as the first anti-cancer treatment not part of the study arm for a given participant, or death, whichever occurs first. The nonparametric Kaplan-Meier method was used to estimate the survival curves. The analysis population included all randomized participants.

End point type	Secondary

End point timeframe:

Up to ~26 months

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	264		
Units: Months				
median (confidence interval 95%)	7.2 (6.7 to 8.1)	5.7 (5.0 to 7.1)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA

Statistical analysis description:

Treatment difference in TFTS assessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.

Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent monotherapy (NHA)

Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.03

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is defined as the time from first documented evidence of CR or PR until progressive disease (PD) or death. Per PCWG-modified RECIST 1.1, PD is defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of ≥ 2 new bone lesions is also considered PD. The analysis population included all randomized participants who experience a confirmed CR or PR and had measurable disease at baseline. DOR as assessed by BICR is presented. 9999 = upper limit not reached at the time of data cut-off due to insufficient number of responding participants with relapse.

End point type	Secondary

End point timeframe:

Up to ~26 months

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	7		
Units: Months				
median (confidence interval 95%)	8.1 (6.2 to 14.1)	8.5 (5.2 to 9999)		

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 randomization to PSA progression. PSA progression date is defined as the date of:
1) ≥25% increase and ≥2 ng/mL above the nadir, confirmed by a second value ≥3 weeks later if there is PSA decline from baseline, OR 2) ≥25% increase and ≥2 ng/mL increase from baseline beyond 12

weeks if there is no PSA decline from baseline. The nonparametric Kaplan-Meier method was used to estimate the survival curves. The analysis population included all randomized participants.

End point type	Secondary

End point timeframe:

Up to ~31 months

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	264		
Units: Months				
median (confidence interval 95%)	3.3 (3.0 to 3.5)	3.5 (3.2 to 4.3)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA

Statistical analysis description:

Treatment difference in Time to PSA progression assessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.

Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent monotherapy (NHA)
Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.38

Secondary: Time to First Symptomatic Skeletal-Related Event (SSRE)

End point title	Time to First Symptomatic Skeletal-Related Event (SSRE)

End point description:

SSRE is defined as the time from randomization to the first symptomatic skeletal-related event, defined as whichever occurs first:
- First use of external-beam radiation therapy (EBRT) to prevent or relieve skeletal symptoms;
- Occurrence of new symptomatic pathologic bone fracture (vertebral or nonvertebral);
- Occurrence of spinal cord compression; or
- Tumor-related orthopedic surgical intervention

The analysis population included all randomized participants. 9999 = lower limit, median and upper limit not reached at the time of data cut-off due to insufficient number of responding participants with relapse.

End point type	Secondary
End point timeframe:	
Up to ~31 months	

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	264		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (19.1 to 9999)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA
Statistical analysis description:	
Treatment difference in Time to first SSRE assessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.	
Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent monotherapy (NHA)
Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.78

Secondary: Time to Radiographic Soft Tissue Progression

End point title	Time to Radiographic Soft Tissue Progression
End point description:	
Time to radiographic soft tissue progression is defined as the time from randomization to radiographic soft tissue progression per soft tissue rule of PCWG-modified RECIST 1.1. Progression is defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. Time to radiographic soft tissue progression as assessed by BICR is presented. The analysis population included all randomized participants.	
End point type	Secondary
End point timeframe:	
Up to ~31 months	

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	264		
Units: Months				
median (confidence interval 95%)	10.3 (8.3 to 12.3)	6.4 (6.1 to 10.2)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA
Statistical analysis description:	
Treatment difference in Time to radiographic soft tissue progression assessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.	
Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent monotherapy (NHA)
Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1

Secondary: Time to Pain Progression (TTPP)

End point title	Time to Pain Progression (TTPP)
End point description:	
TTPP is defined as the time from randomization to pain progression as determined by Item 3 of the Brief Pain Inventory Short Form (BPI-SF) and by the Analgesic Quantification Algorithm (AQA) score. Pain progression is defined as: 1) For participants who are asymptomatic at baseline, a ≥2-point change from baseline in the average (4-7 days) BPI-SF item 3 score at 2 consecutive visits OR initiation of opioid use for pain 2) For participants who are symptomatic at baseline (average BPI-SF Item 3 score >0 and/or currently taking opioids), a ≥2-point change from baseline in the average BPI-SF Item 3 score and an average worst pain score ≥4 and no decrease in average opioid use (≥1-point decrease in AQA score from a starting value of 2 or higher) OR any increase in opioid use at 2 consecutive follow-up visits. The analysis population included all participants who have at least 1 assessment available and have received at least 1 dose of study intervention. 9999 = upper limit not reached.	
End point type	Secondary
End point timeframe:	
Up to ~31 months	

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	504	246		
Units: Months				
median (confidence interval 95%)	13.5 (9.7 to 9999)	12.0 (10.1 to 9999)		

Statistical analyses

Statistical analysis title	Pembrolizumab + Olaparib vs NHA
Statistical analysis description:	
Treatment difference in TTPP assessed by the stratified log-rank test stratified by measurable disease status and prior NHA treatment.	
Comparison groups	Pembrolizumab + Olaparib v Next-generation hormonal agent monotherapy (NHA)
Number of subjects included in analysis	750
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3643
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.26

Secondary: Number of Participants Who Experience an Adverse Event (AE)

End point title	Number of Participants Who Experience an Adverse Event (AE)
End point description:	
An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The analysis population included all randomized participants who received at least 1 dose of study intervention. The number of participants who experienced an adverse event are presented.	
End point type	Secondary
End point timeframe:	
Up to ~55 months	

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	526	256		
Units: Participants	518	238		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinue Study Treatment Due to an Adverse Event (AE)

End point title	Number of Participants Who Discontinue Study Treatment Due to an Adverse Event (AE)

End point description:

An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The analysis population included all randomized participants who received at least 1 dose of study intervention. The number of participants who discontinue study treatment due to an AE are presented.

End point type	Secondary

End point timeframe:

Up to ~1461 Days

End point values	Pembrolizumab + Olaparib	Next-generation hormonal agent monotherapy (NHA)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	526	256		
Units: Participants	90	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to ~55 months

Adverse event reporting additional description:

All-cause mortality: All allocated participants. AEs: All allocated participants who received =1 dose of study intervention. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to study drug are excluded as AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Next-generation hormonal agent monotherapy (NHA)

Reporting group description:

Participants received a single NHA of either abiraterone acetate (participants previously treated with enzalutamide) 1000 mg as two 500 mg or four 250 mg oral tablets once daily (QD) PLUS prednisone or prednisolone 10 mg as one 5 mg tablet BID until progression OR participants received enzalutamide (participants previously treated with abiraterone acetate) 160 mg as four 40 mg oral tablets or capsules OR two 80 mg tablets QD until progression.

Reporting group title	Pembrolizumab + Olaparib

Reporting group description:

Participants received olaparib 600 mg as two 150 mg oral tablets twice daily (BID) continuously until progression PLUS on Day 1 of each 21-day cycle, pembrolizumab 200 mg by intravenous (IV) infusion for up to 35 cycles (approximately 2 years).

Serious adverse events	Next-generation hormonal agent monotherapy (NHA)	Pembrolizumab + Olaparib	
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 256 (23.05%)	179 / 526 (34.03%)	
number of deaths (all causes)	178	372	
number of deaths resulting from adverse events	8	29	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 256 (0.00%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 256 (0.39%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 256 (0.78%)	5 / 526 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 5	
Asthenia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 256 (0.39%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 256 (0.78%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Immune-mediated lung disease			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 256 (0.00%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 256 (0.39%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Fall			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 256 (0.39%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis radiation			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			

subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 256 (0.39%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 256 (0.00%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocarditis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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	0 / 256 (0.00%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery occlusion			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 256 (0.39%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Depressed level of consciousness			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraparesis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 256 (0.00%)	5 / 526 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 256 (0.00%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	3 / 256 (1.17%)	20 / 526 (3.80%)	
occurrences causally related to treatment / all	1 / 3	18 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 256 (0.00%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	0 / 256 (0.00%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mechanical ileus			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatic function abnormal			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder disorder			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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			
Toxic skin eruption			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 256 (0.39%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	4 / 256 (1.56%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelocaliectasis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ureteric stenosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	2 / 256 (0.78%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 256 (0.39%)	5 / 526 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	1 / 256 (0.39%)	9 / 526 (1.71%)	
occurrences causally related to treatment / all	0 / 1	8 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 256 (0.78%)	7 / 526 (1.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 256 (0.00%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myositis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	2 / 256 (0.78%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Dengue fever			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 256 (0.78%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
COVID-19			
subjects affected / exposed	1 / 256 (0.39%)	6 / 526 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Bacteraemia			
subjects affected / exposed	1 / 256 (0.39%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 256 (0.00%)	5 / 526 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Erysipelas			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective spondylitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 256 (0.78%)	15 / 526 (2.85%)	
occurrences causally related to treatment / all	0 / 2	2 / 15	
deaths causally related to treatment / all	0 / 0	1 / 2	
Pneumonia aspiration			
subjects affected / exposed	0 / 256 (0.00%)	2 / 526 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (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	3 / 256 (1.17%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 256 (0.39%)	4 / 526 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 3	
Encephalitis			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	4 / 256 (1.56%)	11 / 526 (2.09%)	
occurrences causally related to treatment / all	0 / 4	1 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 256 (0.78%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
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	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 256 (0.00%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			

subjects affected / exposed	0 / 256 (0.00%)	3 / 526 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 256 (1.17%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 256 (0.39%)	0 / 526 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 256 (0.00%)	1 / 526 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Next-generation hormonal agent monotherapy (NHA)	Pembrolizumab + Olaparib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	215 / 256 (83.98%)	495 / 526 (94.11%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 256 (12.11%)	31 / 526 (5.89%)	
occurrences (all)	32	37	
Hot flush			
subjects affected / exposed	15 / 256 (5.86%)	11 / 526 (2.09%)	
occurrences (all)	15	11	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 256 (2.73%)	52 / 526 (9.89%)	
occurrences (all)	8	61	
Asthenia			

subjects affected / exposed	27 / 256 (10.55%)	95 / 526 (18.06%)	
occurrences (all)	29	109	
Fatigue			
subjects affected / exposed	66 / 256 (25.78%)	188 / 526 (35.74%)	
occurrences (all)	67	200	
Oedema peripheral			
subjects affected / exposed	14 / 256 (5.47%)	48 / 526 (9.13%)	
occurrences (all)	16	51	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 256 (3.52%)	46 / 526 (8.75%)	
occurrences (all)	10	57	
Cough			
subjects affected / exposed	7 / 256 (2.73%)	29 / 526 (5.51%)	
occurrences (all)	7	34	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 256 (5.08%)	24 / 526 (4.56%)	
occurrences (all)	14	26	
Investigations			
Weight decreased			
subjects affected / exposed	15 / 256 (5.86%)	71 / 526 (13.50%)	
occurrences (all)	15	74	
Blood creatinine increased			
subjects affected / exposed	6 / 256 (2.34%)	47 / 526 (8.94%)	
occurrences (all)	6	57	
Blood alkaline phosphatase increased			
subjects affected / exposed	25 / 256 (9.77%)	35 / 526 (6.65%)	
occurrences (all)	28	38	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 256 (3.91%)	40 / 526 (7.60%)	
occurrences (all)	10	49	
Alanine aminotransferase increased			
subjects affected / exposed	7 / 256 (2.73%)	29 / 526 (5.51%)	
occurrences (all)	7	30	
Nervous system disorders			

Headache			
subjects affected / exposed	13 / 256 (5.08%)	29 / 526 (5.51%)	
occurrences (all)	19	36	
Dysgeusia			
subjects affected / exposed	3 / 256 (1.17%)	31 / 526 (5.89%)	
occurrences (all)	3	32	
Dizziness			
subjects affected / exposed	9 / 256 (3.52%)	44 / 526 (8.37%)	
occurrences (all)	9	53	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	36 / 256 (14.06%)	272 / 526 (51.71%)	
occurrences (all)	38	327	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	18 / 256 (7.03%)	92 / 526 (17.49%)	
occurrences (all)	20	149	
Nausea			
subjects affected / exposed	47 / 256 (18.36%)	223 / 526 (42.40%)	
occurrences (all)	51	280	
Diarrhoea			
subjects affected / exposed	21 / 256 (8.20%)	103 / 526 (19.58%)	
occurrences (all)	25	135	
Constipation			
subjects affected / exposed	44 / 256 (17.19%)	108 / 526 (20.53%)	
occurrences (all)	47	124	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 256 (1.17%)	37 / 526 (7.03%)	
occurrences (all)	3	47	
Pruritus			
subjects affected / exposed	6 / 256 (2.34%)	39 / 526 (7.41%)	
occurrences (all)	6	44	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	11 / 256 (4.30%)	27 / 526 (5.13%)	
occurrences (all)	14	35	

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 256 (1.56%)	54 / 526 (10.27%)	
occurrences (all)	4	55	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	23 / 256 (8.98%)	36 / 526 (6.84%)	
occurrences (all)	31	40	
Myalgia			
subjects affected / exposed	8 / 256 (3.13%)	33 / 526 (6.27%)	
occurrences (all)	10	36	
Arthralgia			
subjects affected / exposed	37 / 256 (14.45%)	99 / 526 (18.82%)	
occurrences (all)	46	122	
Back pain			
subjects affected / exposed	45 / 256 (17.58%)	85 / 526 (16.16%)	
occurrences (all)	52	95	
Bone pain			
subjects affected / exposed	26 / 256 (10.16%)	35 / 526 (6.65%)	
occurrences (all)	27	43	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 256 (5.08%)	26 / 526 (4.94%)	
occurrences (all)	16	33	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	46 / 256 (17.97%)	155 / 526 (29.47%)	
occurrences (all)	53	178	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2019	Amendment 1 addressed administrative updates to address health authority requests and minor administrative changes throughout the protocol to ensure consistency and clarity.
20 November 2019	Amendment 2 addressed administrative updates to add missing standard safety causality/intensity language in Appendix 3 that was inadvertently truncated during publishing of the original protocol, and to correct the duplicate numbering of exclusion criterion #12 during publishing of the PA01. Minor administrative changes were also identified after Protocol Amendment 1 to ensure consistency and clarity throughout the protocol.
04 May 2021	Amendment 4 addressed administrative updates to incorporate recently authored protocol template language for Verification of Progression (VOP) related to rPFS endpoint with BICR and to update IMP/NIMP classification of active comparators based on guidance issued by European Commission. Minor administrative changes were also included to insure consistency and clarity throughout the protocol.
23 September 2021	Amendment 5 addressed a contraindication for concurrent administration of abiraterone and radium-223 during abiraterone treatment, an addition of a consideration for dose reduction of medicinal products that are metabolized by CYP2D6 and have a narrow therapeutic index to potentially prolong the QT interval, and minor administrative changes to ensure consistency and clarity throughout the protocol.
13 June 2022	Amendment 6 addressed the recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study due to futility.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported