Clinical trial results:
A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound)

Summary

EudraCT number	2016-000300-28
Trial protocol	SE DK NO ES AT FR IT
Global end of trial date	20 March 2020

Results information

Result version number	v1 (current)
This version publication date	21 October 2023
First version publication date	21 October 2023

Trial information

Trial identification

Sponsor protocol code	D081DC00007

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Clinical Study Information Center
Sponsor organisation address	Melbourn Science Park, Royston, United Kingdom, SG8 6EE
Public contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.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	20 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2020
Global end of trial reached?	Yes
Global end of trial date	20 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint of the study is radiographic progression free survival (rPFS) in subjects with BRCA1, BRCA2 or ATM mutations (Cohort A).

Protection of trial subjects:

Patients given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 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	France: 62
Country: Number of subjects enrolled	Japan: 57
Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Turkey: 30
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 29
Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	United States: 33
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Taiwan: 15
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Norway: 3

Worldwide total number of subjects	387
EEA total number of subjects	131

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)	116
From 65 to 84 years	260
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

Subjects were divided into two cohorts based on HRR gene mutation status. Subjects with mutations in either BRCA1, BRCA2, or ATM are in Cohort A whereas subjects with mutations among 12 other genes involved in the HRR pathway (BARD1, BRIP1, CDK12, CHEK1,CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or RAD54L) are in Cohort B.

Pre-assignment

Screening details:

Consenting subjects were assessed to ensure they met eligibility criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A Olaparib 300mg bd

Arm description:

2x150mg film-coated tablets

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

Dosage and administration details:

300mg twice daily (100mg and 150mg tablets)

Arm title	Cohort A Investigators choice of NHA

Arm description:

either enzalutamide capsules (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone)

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

Dosage and administration details:

160mg once daily (40mg tablets)

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

Dosage and administration details:

1000mg once daily (250mg or 500mg tablets) with prednisone 5mg bd

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

Dosage and administration details:

5mg bd with abiraterone acetate 1000mg od. Prednisolone was permitted for use instead of prednisone

Arm title	Cohort B Olaparib 300mg bd

Arm description:

2x150mg film-coated tablets

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

Dosage and administration details:

300mg twice daily (100mg and 150mg tablets)

Arm title	Cohort B Investigators choice of NHA

Arm description:

either enzalutamide capsules (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone)

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

Dosage and administration details:

160mg once daily (40mg tablets)

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

Dosage and administration details:

5mg bd with abiraterone acetate 1000mg od. Prednisolone was permitted for use instead of prednisone

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

Dosage and administration details:

1000mg once daily (250mg or 500mg tablets) with prednisone 5mg bd

Number of subjects in period 1	Cohort A Olaparib 300mg bd	Cohort A Investigators choice of NHA	Cohort B Olaparib 300mg bd
Started	162	83	94
Completed	0	0	0
Not completed	162	83	94
Adverse event, serious fatal	88	54	67
Consent withdrawn by subject	21	7	7
Disease progression	-	-	-
Ongoing study at data cut off	49	21	19
Study terminated by sponsor	1	-	-
Investigator decision	-	1	-
Screen failure	-	-	-
Lost to follow-up	3	-	1

Number of subjects in period 1	Cohort B Investigators choice of NHA
Started	48
Completed	0
Not completed	48
Adverse event, serious fatal	28
Consent withdrawn by subject	6
Disease progression	1
Ongoing study at data cut off	12
Study terminated by sponsor	-
Investigator decision	-
Screen failure	1
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A Olaparib 300mg bd
Reporting group description:	
2x150mg film-coated tablets	
Reporting group title	Cohort A Investigators choice of NHA
Reporting group description:	
either enzalutamide capsules (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone)	
Reporting group title	Cohort B Olaparib 300mg bd
Reporting group description:	
2x150mg film-coated tablets	
Reporting group title	Cohort B Investigators choice of NHA
Reporting group description:	
either enzalutamide capsules (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone)	

Reporting group values	Cohort A Olaparib 300mg bd	Cohort A Investigators choice of NHA	Cohort B Olaparib 300mg bd
Number of subjects	162	83	94
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)	54	23	28
From 65-84 years	105	59	64
85 years and over	3	1	2
Age Continuous Units: Years			
arithmetic mean	68.0	68.1	69.2
standard deviation	± 8.23	± 7.36	± 8.79
Sex: Female, Male Units: Participants			
Female	0	0	0
Male	162	83	94
Race/Ethnicity, Customized Units: Subjects			
White	109	55	54
Black or African American	2	1	5
Asian	43	19	26
Other	1	1	1
Missing	7	7	8

Reporting group values	Cohort B Investigators choice of NHA	Total	
Number of subjects	48	387	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	116	
From 65-84 years	35	263	
85 years and over	2	8	
Age Continuous			
Units: Years			
arithmetic mean	70.3		
standard deviation	± 7.83	-	
Sex: Female, Male			
Units: Participants			
Female	0	0	
Male	48	387	
Race/Ethnicity, Customized			
Units: Subjects			
White	30	248	
Black or African American	0	8	
Asian	17	105	
Other	0	3	
Missing	1	23	

End points

End points reporting groups

Reporting group title	Cohort A Olaparib 300mg bd
Reporting group description: 2x150mg film-coated tablets	
Reporting group title	Cohort A Investigators choice of NHA
Reporting group description: either enzalutamide capsules (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone)	
Reporting group title	Cohort B Olaparib 300mg bd
Reporting group description: 2x150mg film-coated tablets	
Reporting group title	Cohort B Investigators choice of NHA
Reporting group description: either enzalutamide capsules (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone)	
Subject analysis set title	Cohort A+B Olaparib 300mg bd
Subject analysis set type	Full analysis
Subject analysis set description: Subjects with HRR qualifying mutations (Cohort A+B)	
Subject analysis set title	Cohort A+B Investigators Choice of NHA
Subject analysis set type	Full analysis
Subject analysis set description: Subjects with HRR qualifying mutations (Cohort A+B)	

Primary: Radiological Progression Free Survival (rPFS) by blinded independent central review (BICR) - Cohort A only

End point title	Radiological Progression Free Survival (rPFS) by blinded independent central review (BICR) - Cohort A only[1]

End point description:

The time from randomisation until the date of objective radiological disease progression (determined by RECIST 1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG-3) (bone)) or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression. Progression is defined using (i) Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for soft tissue, as a >=20% increase in the sum of diameters of target lesions and an absolute increase of >=5mm taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters; (ii) Prostate Cancer Working Group 3 (PGWG-3) for bone as >= 2 new bone lesions on the 1st week 8 scan compared to baseline. The confirmatory scan, >=6 weeks later, must show >=2 more new bone lesions (for a total of >=4 new bone lesions since baseline).

End point type	Primary

End point timeframe:

Tumor assessments every 8 weeks from randomisation until radiographic progression assessed by BICR (median duration of treatment of 7 and 4 months for Olaparib and Investigators Choice of NHA respectively).

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study was designed to formally test these endpoints in only Cohort A patients, there is just 1 endpoint that is formally tested for both Cohort A and Cohort B which is rPFS. All other analyses are descriptive only

End point values	Cohort A Olaparib 300mg bd	Cohort A Investigators choice of NHA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	83		
Units: Months				
median (confidence interval 95%)	7.39 (6.24 to 9.33)	3.55 (1.91 to 3.71)		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
Radiological Progression Free Survival (rPFS) by blinded independent central review (BICR)	
Comparison groups	Cohort A Olaparib 300mg bd v Cohort A Investigators choice of NHA
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.47

Notes:

[2] - Cohort A

[3] - 2-sided

Secondary: Confirmed Objective Response Rate (ORR) by blinded independent central review (BICR) - Cohort A only

End point title	Confirmed Objective Response Rate (ORR) by blinded independent central review (BICR) - Cohort A only[4]

End point description:

ORR is the percentage of patients with at least one visit response of Complete response (CR) or Partial response (PR), in their soft tissue disease assessed by Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), in the absence of progression on bone scan assessed by Prostate Cancer Working Group 3 (PCWG3)). Per RECIST v1.1, CR=Disappearance of all target lesions; PR = >=30% decrease in the sum of diameters of target lesions; For each treatment group, ORR is the number of patients with a CR and PR.

End point type	Secondary

End point timeframe:

Tumor assessments every 8 weeks from randomisation until radiographic progression assessed by BICR (median duration of treatment of 7 and 4 months for Olaparib and Investigators Choice of NHA respectively).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study was designed to formally test these endpoints in only Cohort A patients, there is just 1 endpoint that is formally tested for both Cohort A and Cohort B which is rPFS. All other analyses are descriptive only

End point values	Cohort A Olaparib 300mg bd	Cohort A Investigators choice of NHA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	43		
Units: Participants				
Response	28	1		
No response	56	42		

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Cohort A Olaparib 300mg bd v Cohort A Investigators choice of NHA
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	20.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.18
upper limit	379.18

Notes:

[5] - Cohort A

Secondary: Radiological Progression Free Survival (rPFS) by blinded independent central review (BICR) - Cohort A+B

End point title	Radiological Progression Free Survival (rPFS) by blinded independent central review (BICR) - Cohort A+B

End point description:

The time from randomisation until the date of objective radiological disease progression (by RECIST 1.1 and Prostate Cancer Working Group 3 (PGWG-3)) or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression.

End point type	Secondary

End point timeframe:

Tumor assessments every 8 weeks from randomisation until radiographic progression assessed by BICR (median duration of treatment of 7 and 4 months for Olaparib and Investigators Choice of NHA respectively).

End point values	Cohort A+B Olaparib 300mg bd	Cohort A+B Investigators Choice of NHA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	256	131		
Units: Months				
median (confidence interval 95%)	5.82 (5.52 to 7.36)	3.52 (2.2 to 3.65)		

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Cohort A+B Investigators Choice of NHA v Cohort A+B Olaparib 300mg bd
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.63

Notes:

[6] - Cohort A+B

Secondary: Overall Survival (OS) - Cohort A only

End point title	Overall Survival (OS) - Cohort A only[7]

End point description:

Number of Participants with Overall Survival (OS) - Cohort A only.

End point type	Secondary

End point timeframe:

Approximately 35 months after the first patient was randomised.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study was designed to formally test these endpoints in only Cohort A patients, there is just 1 endpoint that is formally tested for both Cohort A and Cohort B which is rPFS. All other analyses are descriptive only

End point values	Cohort A Olaparib 300mg bd	Cohort A Investigators choice of NHA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	83		
Units: Participants				
Died	91	57		
Alive at data cut-off	49	21		

Terminated prior to death (withdrawn consent)	22	5		

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Cohort A Olaparib 300mg bd v Cohort A Investigators choice of NHA
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0175
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.97

Notes:

[8] - Cohort A

Secondary: Time to pain progression - Cohort A only

End point title	Time to pain progression - Cohort A only[9]

End point description:

Time from randomisation to time point at which worsening in pain is observed (ie date of pain progression - date of randomisation + 1). Based on average Brief Pain Inventory - short form (BPI-SF) worst pain [Item 3] and Analgesic Quantification Algorithm [AQA] score.

End point type	Secondary

End point timeframe:

Every 4 weeks from randomisation (for 7 consecutive days) throughout the study (median duration of treatment of 7 and 4 months for Olaparib and Investigators Choice of NHA respectively).

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The study was designed to formally test these endpoints in only Cohort A patients, there is just 1 endpoint that is formally tested for both Cohort A and Cohort B which is rPFS. All other analyses are descriptive only

End point values	Cohort A Olaparib 300mg bd	Cohort A Investigators choice of NHA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	83		
Units: Months				
median (confidence interval 95%)	99999999 (-99999999 to 99999999)	9.92 (5.39 to 99999999)		

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Cohort A Olaparib 300mg bd v Cohort A Investigators choice of NHA
Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0192
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.91

Notes:

[10] - Cohort A

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time of signature of informed consent throughout the treatment period (median duration of treatment of 7.5 and 3.9 months for Olaparib and Investigators Choice of NHA respectively) up to and including the 30-day follow-up period

Adverse event reporting additional description:

131 subjects randomised to Investigators Choice of NHA (IC) group (Full Analysis Set), however 1 subject did not receive treatment (resulting in 130 in Safety Analysis Set). Hence for IC group, Total number at risk for all-cause mortality = 131, Total # at Risk by any Serious Adverse Event = 130 and Total # at Risk by any Other Adverse Event = 130

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Cohort A+B Investigators choice of NHA

Reporting group description:

either enzalutamide capsules (160 mg od) or abiraterone acetate tablets (1,000 mg od with 5 mg bid prednisone)

Reporting group title	Cohort A+B Olaparib 300mg bd

Reporting group description:

2x150mg film-coated tablets

Serious adverse events	Cohort A+B Investigators choice of NHA	Cohort A+B Olaparib 300mg bd	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 130 (30.00%)	94 / 256 (36.72%)	
number of deaths (all causes)	88	160	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transitional cell carcinoma			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioma			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric cancer			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial thrombosis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Phlebitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
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			
Asthenia			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	4 / 256 (1.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 130 (1.54%)	3 / 256 (1.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (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			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	3 / 256 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Interstitial lung disease			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	4 / 256 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	5 / 256 (1.95%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
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			
Ankle fracture			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis radiation			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 130 (1.54%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	3 / 256 (1.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis radiation			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post-traumatic pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary ostial stenosis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 130 (0.77%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Right ventricular failure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiomyopathy			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 130 (1.54%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	3 / 256 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ballismus			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
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			
Pancytopenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	4 / 256 (1.56%)	
occurrences causally related to treatment / all	0 / 0	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	23 / 256 (8.98%)	
occurrences causally related to treatment / all	0 / 0	18 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	3 / 256 (1.17%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Eye disorders			
Diplopia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	2 / 130 (1.54%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhoea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	4 / 256 (1.56%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress ulcer			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Budd-Chiari syndrome			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Drug eruption			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 130 (1.54%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	3 / 256 (1.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephrolithiasis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 130 (1.54%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			

alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Cystitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	4 / 130 (3.08%)	5 / 256 (1.95%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 130 (2.31%)	3 / 256 (1.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 130 (3.08%)	11 / 256 (4.30%)	
occurrences causally related to treatment / all	0 / 4	2 / 13	
deaths causally related to treatment / all	0 / 3	1 / 3	
Pharyngitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pneumocystis jirovecii pneumoni			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 130 (2.31%)	0 / 256 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	0 / 130 (0.00%)	1 / 256 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 130 (0.00%)	2 / 256 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort A+B Investigators choice of NHA	Cohort A+B Olaparib 300mg bd	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 130 (86.15%)	241 / 256 (94.14%)	
Investigations			
Weight decreased			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	7 / 130 (5.38%)	21 / 256 (8.20%)	
occurrences (all)	7	21	
Nervous system disorders			
Headache			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 130 (2.31%)	16 / 256 (6.25%)	
occurrences (all)	3	29	
Dysgeusia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 130 (1.54%)	18 / 256 (7.03%)	
occurrences (all)	2	20	
Dizziness			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	5 / 130 (3.85%)	17 / 256 (6.64%)	
occurrences (all)	5	18	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	20 / 130 (15.38%)	110 / 256 (42.97%)	
occurrences (all)	23	154	
Neutropenia			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	0 / 130 (0.00%)	13 / 256 (5.08%)	
occurrences (all)	0	16	
Lymphopenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	1 / 130 (0.77%)	13 / 256 (5.08%)	
occurrences (all)	1	15	
Thrombocytopenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	2 / 130 (1.54%)	18 / 256 (7.03%)	
occurrences (all)	2	22	
General disorders and administration site conditions			
Oedema peripheral			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	10 / 130 (7.69%)	34 / 256 (13.28%)	
occurrences (all)	10	36	
Pyrexia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 130 (3.08%)	15 / 256 (5.86%)	
occurrences (all)	4	16	
Fatigue			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	28 / 130 (21.54%)	68 / 256 (26.56%)	
occurrences (all)	28	71	
Asthenia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	18 / 130 (13.85%)	37 / 256 (14.45%)	
occurrences (all)	19	54	
Gastrointestinal disorders			
Constipation			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	19 / 130 (14.62%)	49 / 256 (19.14%)	
occurrences (all)	21	52	
Dyspepsia			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	3 / 130 (2.31%)	20 / 256 (7.81%)	
occurrences (all)	3	23	
Diarrhoea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	9 / 130 (6.92%)	54 / 256 (21.09%)	
occurrences (all)	9	71	
Vomiting			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	17 / 130 (13.08%)	49 / 256 (19.14%)	
occurrences (all)	19	82	
Nausea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	26 / 130 (20.00%)	109 / 256 (42.58%)	
occurrences (all)	28	136	
Stomatitis			
subjects affected / exposed	2 / 130 (1.54%)	13 / 256 (5.08%)	
occurrences (all)	2	14	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	3 / 130 (2.31%)	29 / 256 (11.33%)	
occurrences (all)	3	32	
Dyspnoea			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 130 (3.08%)	24 / 256 (9.38%)	
occurrences (all)	4	25	
Psychiatric disorders			
Insomnia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	4 / 130 (3.08%)	14 / 256 (5.47%)	
occurrences (all)	4	14	
Renal and urinary disorders			
Haematuria			
alternative dictionary used: MedDRA 22.0			

subjects affected / exposed	10 / 130 (7.69%)	6 / 256 (2.34%)	
occurrences (all)	11	7	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	14 / 130 (10.77%)	25 / 256 (9.77%)	
occurrences (all)	16	26	
Back pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	17 / 130 (13.08%)	36 / 256 (14.06%)	
occurrences (all)	18	44	
Musculoskeletal pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	6 / 130 (4.62%)	17 / 256 (6.64%)	
occurrences (all)	6	18	
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	6 / 130 (4.62%)	14 / 256 (5.47%)	
occurrences (all)	7	14	
Pain in extremity			
subjects affected / exposed	6 / 130 (4.62%)	14 / 256 (5.47%)	
occurrences (all)	6	18	
Infections and infestations			
Urinary tract infection			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	12 / 130 (9.23%)	18 / 256 (7.03%)	
occurrences (all)	15	22	
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 22.0			
subjects affected / exposed	24 / 130 (18.46%)	78 / 256 (30.47%)	
occurrences (all)	25	88	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2017	Version 2.0: Administration of other anti-cancer agents: remove following text "corticosteroids for the symptomatic control of brain metastases" because subjects with known brain metastases are excluded from the study
04 June 2018	Version 3.0: Abiraterone acetate 500mg tablets added to treatment regimens

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported