Clinical trial results:
A Phase 3, Randomized, Double-blind Study of Pembrolizumab (MK-3475) Plus Docetaxel Plus Prednisone versus Placebo Plus Docetaxel Plus Prednisone in Participants with Chemotherapy naïve Metastatic Castration-Resistant Prostate Cancer (mCRPC) who have Progressed on a Next Generation Hormonal Agent (NHA) (KEYNOTE-921)

Summary

EudraCT number	2018-004116-22
Trial protocol	AT DE NL GB ES FR IE IT
Global end of trial date	18 July 2023

Results information

Result version number	v1 (current)
This version publication date	06 July 2024
First version publication date	06 July 2024

Trial information

Trial identification

Sponsor protocol code	MK-3475-921

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03834506
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: KEYNOTE-921

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@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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	18 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2022
Global end of trial reached?	Yes
Global end of trial date	18 July 2023
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 pembrolizumab (MK-3475) and docetaxel in the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) who have not received chemotherapy for mCRPC but have progressed on or are intolerant to Next Generation Hormonal Agent (NHA).

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	Argentina: 53
Country: Number of subjects enrolled	Australia: 33
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Brazil: 16
Country: Number of subjects enrolled	Canada: 57
Country: Number of subjects enrolled	Chile: 20
Country: Number of subjects enrolled	China: 21
Country: Number of subjects enrolled	Colombia: 55
Country: Number of subjects enrolled	France: 135
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Ireland: 16
Country: Number of subjects enrolled	Israel: 34
Country: Number of subjects enrolled	Italy: 51
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Netherlands: 56
Country: Number of subjects enrolled	Russian Federation: 71
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Taiwan: 12

Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	United States: 87
Worldwide total number of subjects	1030
EEA total number of subjects	423

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)	225
From 65 to 84 years	793
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 1030 participants randomized in the MK-3475-921 global study, 21 participants were also included in the China extension study for MK-3475-921 (NCT04907227).

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pembrolizumab + Docetaxel

Arm description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg via IV infusion

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	TAXOTERE®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

docetaxel 75 mg/m^2 by IV infusion

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

Dosage and administration details:

5 mg by oral tablets

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	DECADRON®
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

8 mg by oral tablets

Arm title	Placebo + Docetaxel

Arm description:

Participants received placebo by IV infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.

Arm type	Placebo Comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	TAXOTERE®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

docetaxel 75 mg/m^2 by IV infusion

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	DECADRON®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

8 mg by oral tablets

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

Dosage and administration details:

5 mg by oral tablets

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Normal saline or dextrose infusion
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose-matched placebo by IV infusion

Number of subjects in period 1	Pembrolizumab + Docetaxel	Placebo + Docetaxel
Started	515	515
Treated	514	514
Completed	0	0
Not completed	515	515
Consent withdrawn by subject	10	8

Physician decision	3	1
Death	336	326
Withdrawal by Parent/Guardian	1	1
Sponsor decision	165	178
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pembrolizumab + Docetaxel
Reporting group description:	
Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.	
Reporting group title	Placebo + Docetaxel
Reporting group description:	
Participants received placebo by IV infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.	

Reporting group values	Pembrolizumab + Docetaxel	Placebo + Docetaxel	Total
Number of subjects	515	515	1030
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)	120	105	225
From 65-84 years	386	407	793
85 years and over	9	3	12
Age Continuous Units: Years			
arithmetic mean	69.9	70.4	
standard deviation	± 7.9	± 7.1	-
Sex: Female, Male Units: Participants			
Female	0	0	0
Male	515	515	1030
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	6	8	14
Asian	78	76	154
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	13	13	26
White	401	399	800
More than one race	15	18	33
Unknown or Not Reported	1	1	2

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	79	77	156
Not Hispanic or Latino	402	393	795
Unknown or Not Reported	34	45	79
Prior Treatment with a Next Generation Hormonal Agent (NHA): Abiraterone Acetate			
Participants were stratified according to prior treatment with abiraterone acetate. Participants were eligible for the study if they had received prior treatment with a NHA (abiraterone acetate) for metastatic hormone-sensitive prostate cancer (mHSPC) or metastatic castration-resistant prostate cancer (CRPC) and either progressed after treatment or became intolerant of the drug.			
Units: Subjects			
Yes: Prior Treatment with NHA	278	277	555
No: Prior Treatment with NHA	237	238	475
Type of Metastases at Baseline			
Participants were stratified by the type of metastases present at baseline determined by blinded independent central review. If the metastases were only in the bone the participants were categorized as bone only. If the metastases were not in the bone, but in the liver, participants were categorized as liver. All other participants were categorized as other.			
Units: Subjects			
Bone only	268	239	507
Liver	34	33	67
Other	213	243	456
Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)			
Participants were classified by ECOG PS defined as: ECOG=0: Fully active, able to carry out all pre-disease performance with no restriction; ECOG=1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; ECOG=2: Ambulatory and capable of all self-care but unable to carry out work activities, up and about >50% of waking hours; ECOG=3: Capable of only limited self-care, confined to bed or chair >50% of waking hours; ECOG=4: Completely disabled, cannot carry out self-care, totally confined to bed or chair; ECOG=5: Dead			
Units: Subjects			
ECOG = 0	298	286	584
ECOG = 1	212	227	439
ECOG = 2	0	0	0
ECOG = 3	0	0	0
ECOG = 4	1	0	1
ECOG = 5	0	0	0
Missing	4	2	6

End points

End points reporting groups

Reporting group title	Pembrolizumab + Docetaxel

Reporting group description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.

Reporting group title	Placebo + Docetaxel

Reporting group description:

Participants received placebo by IV infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from randomization to death due to any cause. The OS was calculated using the product-limit Kaplan-Meier (K-M) method for censored data. Participants without documented death at the time of the analysis were censored at the date of the last follow-up. This was analyzed in all randomized participants in the intent to treat (ITT) population who had data available.

End point type	Primary

End point timeframe:

Up to 36.5 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	515		
Units: Months				
median (confidence interval 95%)	19.6 (18.2 to 20.9)	19.0 (17.9 to 20.9)		

Statistical analyses

Statistical analysis title	OS
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.1677 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.09

Notes:

[1] - HR based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior treatment with a NHA (abiraterone acetate) and type of metastases at baseline.

[2] - One-sided p-value based on log-rank test stratified by prior treatment with a NHA (abiraterone acetate) and type of metastases at baseline.

Primary: Radiographic Progression-free Survival (rPFS) Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	Radiographic Progression-free Survival (rPFS) Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point description:

rPFS was defined as the time from randomization to occurrence of: radiological tumor progression using RECIST 1.1 as assessed by BICR; progression of bone lesions using PCWG criteria; or death due to any cause. Radiological progression as per RECIST 1.1 was ≥20% increase in sum of diameters of target lesions and progression of existing non-target lesions. Progression of bone lesions by PCWG criteria was the appearance of ≥2 new bone lesions on bone scan, that have been confirmed to not represent tumor flare, and was persistent for ≥6 weeks. The rPFS was calculated using the product-limit K-M method for censored data. Participants without a rPFS event were censored at the date of last disease assessment. This was analyzed in all randomized participants in the ITT population who had data available.

End point type	Primary

End point timeframe:

Up to approximately 28 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	515		
Units: Months				
median (confidence interval 95%)	8.6 (8.3 to 10.2)	8.3 (8.2 to 8.5)		

Statistical analyses

Statistical analysis title	rPFS
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0335 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.01

Notes:

[3] - HR based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

[4] - One-sided p-value based on log-rank test stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

Secondary: Prostate-specific Antigen (PSA) Response Rate

End point title	Prostate-specific Antigen (PSA) Response Rate

End point description:

The Prostate-specific Antigen (PSA) response rate was the percentage of participants who had PSA response defined as a reduction in the PSA level from baseline by ≥50%. The reduction in PSA level was confirmed by an additional PSA evaluation performed ≥3 weeks from the original response. The analysis was performed on participants who had baseline PSA measurements. This was analyzed in all randomized participants in the ITT population, who had a PSA measurement at baseline, and had data available.

End point type	Secondary

End point timeframe:

Up to 36.5 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	486		
Units: Percentage of participants				
number (confidence interval 95%)	44.5 (40.0 to 49.1)	45.7 (41.2 to 50.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	Objective Response Rate (ORR) Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point description:

ORR was 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) on bone scan per PCWG) or partial response (PR: at least a 30% decrease in the sum of diameters of target lesions per RECIST 1.1; and non-progressive disease, non-evaluable [NE], or NED on bone scan or CR with non-progressive disease or NE bone scan per PCWG). This was analyzed in all randomized participants in the ITT population, with measurable disease at baseline, who had data available.

End point type	Secondary

End point timeframe:

Up to 36.5 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	203	221		
Units: Percentage of participants				
number (confidence interval 95%)	33.5 (27.0 to 40.4)	35.3 (29.0 to 42.0)		

Statistical analyses

Statistical analysis title	ORR
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6545 [5]
Method	Miettinen & Nurminen method
Parameter estimate	Percent Difference
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	7.1

Notes:

[5] - Based on Miettinen & Nurminen method stratified by prior treatment with a NHA (abiraterone acetate) and type of metastases at baseline.

Secondary: Time to Initiation of the First Subsequent Anti-cancer Therapy (TFST)

End point title	Time to Initiation of the First Subsequent Anti-cancer Therapy (TFST)

End point description:

TFST was defined as the time from randomization to initiation of the first subsequent anti-cancer therapy or death; whichever occurred first. The TFST was calculated using the product-limit K-M method for censored data. Any participant not known to have further subsequent therapy or death was censored at the last known time that no subsequent new anti-cancer therapy was received. This was analyzed in all randomized participants in the ITT population who had data available.

End point type	Secondary

End point timeframe:

Up to approximately 28 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	515		
Units: Months				
median (confidence interval 95%)	10.7 (10.4 to 11.1)	10.4 (9.7 to 11.1)		

Statistical analyses

Statistical analysis title	TFST
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.0331 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.01

Notes:

[6] - HR based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

[7] - One-sided p-value based on log-rank test stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

Secondary: Duration of Response (DOR) Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	Duration of Response (DOR) Per Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point description:

DOR was the time from first evidence of complete response (CR: disappearance of all target lesions per RECIST 1.1; and no evidence of disease [NED] on bone scan per PCWG) or partial response (PR: ≥30% decrease in the sum of diameters of target lesions per RECIST 1.1; and non-progressive disease, non-evaluable [NE], or NED on bone scan or CR with non-progressive disease or NE bone scan per PCWG) until progressive disease (PD) or death. PD was ≥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 ≥5 mm. PD per PCWG was the appearance of ≥2 new bone lesions on bone scan that don’t represent tumor flare and persisted for ≥6 weeks. The DOR was calculated using the product-limit K-M method. Participants who did not progress were censored at the date of last assessment. This was analyzed in all randomized participants in the ITT population, who had CR or PR, and data available.

End point type	Secondary
End point timeframe: Up to 36.5 months	

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	78		
Units: Months				
median (confidence interval 95%)	6.3 (6.1 to 7.8)	6.2 (6.2 to 6.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression (TTPP) as Assessed by Brief Pain Inventory-Short Form (BPI-SF) Item 3 ("Worst Pain in 24 Hours") and Opiate Analgesic Use Assessed by the Analgesic Quantification Algorithm (AQA) Score

End point title	Time to Pain Progression (TTPP) as Assessed by Brief Pain Inventory-Short Form (BPI-SF) Item 3 ("Worst Pain in 24 Hours") and Opiate Analgesic Use Assessed by the Analgesic Quantification Algorithm (AQA) Score

End point description:

TTPP was the time from randomization to pain progression (PP) per BPI-SF Item 3 and AQA score. For BPI-SF item 3, participant responses to "Please rate your worst pain in the last 24 hours" are scored from 0 (no pain) to 10 (worst pain). A higher score means greater pain. AQA captures analgesic use, scored from 0 (no analgesic) to 7 (strong use). A higher score means higher intensity of use. Asymptomatic at baseline (BL): PP is ≥2-point change from BL (CBL) in item 3 score OR opioid use initiation. Symptomatic at BL: PP is ≥2-point CBL in Item 3 score, a score of ≥4 and no decrease in average opioid use OR increase in use. Participants with >2 consecutive unevaluable visits were censored at the last assessment. This was analyzed by K-M method in all participants in the patient-reported outcomes (PRO) full analysis set (FAS) who got ≥1 dose of study drug and had PRO data available. 9999: value not reached at time of data cutoff due to insufficient number of participants with an event.

End point type	Secondary
End point timeframe: Up to 36.5 months	

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	507	502		
Units: Months				
median (confidence interval 95%)	21.1 (13.7 to 9999)	9999 (13.8 to 9999)		

Statistical analyses

Statistical analysis title	TTPP
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.6178 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.43

Notes:

[8] - HR based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.
[9] - One-sided p-value based on log-rank test stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

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

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

End point description:

SSRE was the time from randomization to the first symptomatic skeletal-related event defined as:
1. Use of external-beam radiation therapy (EBRT) to prevent or relieve skeletal symptoms
2. Occurrence of new symptomatic pathologic bone fracture (vertebral or non-vertebral)
3. Occurrence of spinal cord compression
4. Tumor-related orthopedic surgical intervention, whichever occurs first.

The SSRE was calculated using the product-limit K-M method for censored data. Participants without symptomatic skeletal-related events were censored at the last evaluable assessment. This was analyzed in all randomized participants in the ITT population who had data available. 9999: Value not reached at time of data cutoff due to insufficient number of participants with an event.

End point type	Secondary

End point timeframe:

Up to 36.5 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	515		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	SSRE
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.9788 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.33

Notes:

[10] - HR based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.
[11] - One-sided p-value based on log-rank test stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

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

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

End point description:

The time to PSA progression was the time from randomization to PSA progression. The PSA progression date was 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 was PSA decline from baseline; OR
2. ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks if there was no PSA decline from baseline

Time to PSA progression was calculated using the product-limit K-M method for censored data. Participants without PSA progression were censored at the last evaluable assessment. This was analyzed in all randomized participants in the ITT population, who had a PSA measurement at baseline, and had data available.

End point type	Secondary

End point timeframe:

Up to 36.5 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	515		
Units: Months				
median (confidence interval 95%)	6.9 (6.2 to 7.6)	7.0 (6.3 to 7.6)		

Statistical analyses

Statistical analysis title	Time to PSA Progression
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.297 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.12

Notes:

[12] - HR based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

[13] - One-sided p-value based on log-rank test stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

Secondary: Time to Radiographic Soft Tissue Progression Per Soft Tissue Rules of Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point title	Time to Radiographic Soft Tissue Progression Per Soft Tissue Rules of Prostate Cancer Working Group (PCWG)-modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR)

End point description:

The time to radiographic soft tissue progression was defined as the time from randomization to radiographic soft tissue progression per soft tissue rules of PCWG-modified RECIST 1.1 as assessed by BICR. Progression was 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 was also considered progression. Time to radiographic soft tissue progression was calculated using the product-limit K-M method for censored data. Participants without radiographic soft tissue progression were censored at the last evaluable assessment. This was analyzed in all randomized participants in the ITT population who had data available.

End point type	Secondary

End point timeframe:

Up to 36.5 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	515	515		
Units: Months				
median (confidence interval 95%)	12.4 (10.7 to 14.9)	11.2 (10.4 to 12.5)		

Statistical analyses

Statistical analysis title	Time to Radiographic Soft Tissue Progression
Comparison groups	Pembrolizumab + Docetaxel v Placebo + Docetaxel
Number of subjects included in analysis	1030
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.2876 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.15

Notes:

[14] - HR based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.
[15] - One-sided p-value based on log-rank test stratified by prior treatment with NHA (abiraterone acetate) and type of metastases at baseline.

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

End point title	Number of Participants Who Experienced an Adverse Event (AE)

End point description:

An AE was any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. This was analyzed in all participants who received ≥1 dose of study treatment. The number of participants who experienced an AE is presented.

End point type	Secondary

End point timeframe:

Up to approximately 30 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	514	514		
Units: Participants	508	505		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Discontinued Study Treatment Due To an Adverse Event (AE)

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

End point description:

An AE was any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. This was analyzed in all participants who received ≥1 dose of study treatment. The number of participants who discontinued study treatment due to an AE is presented.

End point type	Secondary

End point timeframe:

Up to approximately 27 months

End point values	Pembrolizumab + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	514	514		
Units: Participants	150	115		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 48 months

Adverse event reporting additional description:

All-cause mortality: All randomized participants; AEs: all participants who got ≥1 dose of study drug. Per protocol, disease progression of cancer was not considered an AE unless considered related to study drug. Thus, MedDRA preferred terms "Neoplasm progression" (NP), "Malignant NP" and "Disease progression" unrelated to study drug are excluded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo + Docetaxel

Reporting group description:

Participants received placebo by IV infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.

Reporting group title	Pembrolizumab + Docetaxel

Reporting group description:

Participants received pembrolizumab 200 mg by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W) for up to a maximum of 35 cycles (approximately 2 years) PLUS docetaxel 75 mg/m^2 by IV infusion on Day 1 of each 21-day cycle (Q3W) for a maximum of 10 cycles (approximately 7 months). Participants also concomitantly received dexamethasone 8 mg by oral tablets at 12 hours, 3 hours, and 1 hour prior to docetaxel administration and prednisone 5 mg by oral tablets twice daily during each 21-day docetaxel cycle.

Serious adverse events	Placebo + Docetaxel	Pembrolizumab + Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	197 / 514 (38.33%)	212 / 514 (41.25%)	
number of deaths (all causes)	329	343	
number of deaths resulting from adverse events	28	29	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neuroendocrine carcinoma			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell carcinoma			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	2 / 514 (0.39%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery aneurysm			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 514 (0.19%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 514 (0.39%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
General physical health deterioration			
subjects affected / exposed	2 / 514 (0.39%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 514 (0.78%)	6 / 514 (1.17%)	
occurrences causally related to treatment / all	0 / 4	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media allergy			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Benign prostatic hyperplasia			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated lung disease			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 514 (0.78%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 514 (0.00%)	5 / 514 (0.97%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Obstructive airways disorder			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (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	6 / 514 (1.17%)	15 / 514 (2.92%)	
occurrences causally related to treatment / all	5 / 6	15 / 15	
deaths causally related to treatment / all	0 / 0	1 / 1	

Pulmonary embolism			
subjects affected / exposed	8 / 514 (1.56%)	6 / 514 (1.17%)	
occurrences causally related to treatment / all	1 / 8	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pulmonary oedema			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 514 (0.19%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	1 / 1	0 / 1	
Lung disorder			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 514 (0.19%)	4 / 514 (0.78%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood calcium increased			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Cystitis radiation			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (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 / 514 (0.19%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower limb fracture			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (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	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Patella fracture			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion related complication			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sternal fracture			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	3 / 514 (0.58%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary radiation injury			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 514 (0.78%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ventricular fibrillation			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (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	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 514 (0.19%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subendocardial ischaemia			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 514 (0.00%)	6 / 514 (1.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nervous system disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (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	5 / 514 (0.97%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 514 (0.19%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebellar haematoma			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cauda equina syndrome			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 514 (0.97%)	5 / 514 (0.97%)	
occurrences causally related to treatment / all	2 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	22 / 514 (4.28%)	28 / 514 (5.45%)	
occurrences causally related to treatment / all	22 / 23	33 / 34	
deaths causally related to treatment / all	1 / 1	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	7 / 514 (1.36%)	6 / 514 (1.17%)	
occurrences causally related to treatment / all	7 / 8	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotic lymphadenopathy			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anal fissure			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 514 (0.00%)	4 / 514 (0.78%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 514 (0.00%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	9 / 514 (1.75%)	13 / 514 (2.53%)	
occurrences causally related to treatment / all	7 / 10	10 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ulcer			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oroantral fistula			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary incontinence			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	4 / 514 (0.78%)	8 / 514 (1.56%)	
occurrences causally related to treatment / all	0 / 5	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (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	3 / 514 (0.58%)	6 / 514 (1.17%)	
occurrences causally related to treatment / all	1 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hypophysitis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	3 / 514 (0.58%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crowned dens syndrome			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	4 / 514 (0.78%)	4 / 514 (0.78%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	6 / 514 (1.17%)	5 / 514 (0.97%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (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 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	3 / 514 (0.58%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 514 (0.19%)	6 / 514 (1.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			

subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (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			
Abdominal infection			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	6 / 514 (1.17%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
COVID-19 pneumonia			
subjects affected / exposed	6 / 514 (1.17%)	5 / 514 (0.97%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 5	0 / 2	
Catheter site cellulitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 514 (0.58%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial sepsis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningomyelitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis meningococcal			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (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 / 514 (0.00%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 514 (2.33%)	14 / 514 (2.72%)	
occurrences causally related to treatment / all	10 / 14	7 / 14	
deaths causally related to treatment / all	1 / 2	0 / 3	
Pneumonia bacterial			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomembranous colitis			

subjects affected / exposed	2 / 514 (0.39%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 514 (0.39%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	3 / 514 (0.58%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 514 (0.58%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 514 (0.39%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			

subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	4 / 514 (0.78%)	2 / 514 (0.39%)	
occurrences causally related to treatment / all	2 / 4	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Urinary tract infection staphylococcal			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (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 bacterial			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 514 (1.36%)	8 / 514 (1.56%)	
occurrences causally related to treatment / all	0 / 8	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	2 / 514 (0.39%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 514 (0.19%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 514 (0.19%)	0 / 514 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 514 (0.00%)	1 / 514 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 514 (0.19%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 514 (0.19%)	3 / 514 (0.58%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Docetaxel	Pembrolizumab + Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	488 / 514 (94.94%)	496 / 514 (96.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	29 / 514 (5.64%)	28 / 514 (5.45%)	
occurrences (all)	32	31	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	42 / 514 (8.17%)	58 / 514 (11.28%)	
occurrences (all)	52	69	
Oedema peripheral			
subjects affected / exposed	106 / 514 (20.62%)	95 / 514 (18.48%)	
occurrences (all)	120	105	
Mucosal inflammation			
subjects affected / exposed	31 / 514 (6.03%)	26 / 514 (5.06%)	
occurrences (all)	34	31	
Fatigue			
subjects affected / exposed	184 / 514 (35.80%)	183 / 514 (35.60%)	
occurrences (all)	224	255	
Asthenia			

subjects affected / exposed	128 / 514 (24.90%)	132 / 514 (25.68%)	
occurrences (all)	201	180	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	59 / 514 (11.48%)	61 / 514 (11.87%)	
occurrences (all)	63	66	
Cough			
subjects affected / exposed	36 / 514 (7.00%)	47 / 514 (9.14%)	
occurrences (all)	39	53	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	46 / 514 (8.95%)	43 / 514 (8.37%)	
occurrences (all)	46	51	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	49 / 514 (9.53%)	47 / 514 (9.14%)	
occurrences (all)	112	107	
Blood alkaline phosphatase increased			
subjects affected / exposed	25 / 514 (4.86%)	28 / 514 (5.45%)	
occurrences (all)	26	28	
Aspartate aminotransferase increased			
subjects affected / exposed	24 / 514 (4.67%)	29 / 514 (5.64%)	
occurrences (all)	27	32	
Alanine aminotransferase increased			
subjects affected / exposed	28 / 514 (5.45%)	27 / 514 (5.25%)	
occurrences (all)	30	38	
White blood cell count decreased			
subjects affected / exposed	27 / 514 (5.25%)	32 / 514 (6.23%)	
occurrences (all)	54	60	
Weight decreased			
subjects affected / exposed	29 / 514 (5.64%)	42 / 514 (8.17%)	
occurrences (all)	29	45	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	100 / 514 (19.46%)	132 / 514 (25.68%)	
occurrences (all)	108	143	

Neuropathy peripheral			
subjects affected / exposed	27 / 514 (5.25%)	27 / 514 (5.25%)	
occurrences (all)	30	28	
Headache			
subjects affected / exposed	34 / 514 (6.61%)	38 / 514 (7.39%)	
occurrences (all)	39	49	
Dysgeusia			
subjects affected / exposed	79 / 514 (15.37%)	73 / 514 (14.20%)	
occurrences (all)	85	88	
Dizziness			
subjects affected / exposed	41 / 514 (7.98%)	38 / 514 (7.39%)	
occurrences (all)	49	42	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	37 / 514 (7.20%)	41 / 514 (7.98%)	
occurrences (all)	47	52	
Anaemia			
subjects affected / exposed	126 / 514 (24.51%)	147 / 514 (28.60%)	
occurrences (all)	168	177	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	38 / 514 (7.39%)	33 / 514 (6.42%)	
occurrences (all)	38	35	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	28 / 514 (5.45%)	26 / 514 (5.06%)	
occurrences (all)	32	30	
Constipation			
subjects affected / exposed	85 / 514 (16.54%)	110 / 514 (21.40%)	
occurrences (all)	99	152	
Vomiting			
subjects affected / exposed	70 / 514 (13.62%)	50 / 514 (9.73%)	
occurrences (all)	90	70	
Stomatitis			
subjects affected / exposed	29 / 514 (5.64%)	34 / 514 (6.61%)	
occurrences (all)	30	43	
Nausea			

subjects affected / exposed	135 / 514 (26.26%)	124 / 514 (24.12%)	
occurrences (all)	194	178	
Diarrhoea			
subjects affected / exposed	184 / 514 (35.80%)	209 / 514 (40.66%)	
occurrences (all)	289	356	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	29 / 514 (5.64%)	23 / 514 (4.47%)	
occurrences (all)	32	24	
Nail discolouration			
subjects affected / exposed	27 / 514 (5.25%)	25 / 514 (4.86%)	
occurrences (all)	28	26	
Nail disorder			
subjects affected / exposed	30 / 514 (5.84%)	30 / 514 (5.84%)	
occurrences (all)	30	30	
Pruritus			
subjects affected / exposed	26 / 514 (5.06%)	46 / 514 (8.95%)	
occurrences (all)	31	53	
Rash			
subjects affected / exposed	54 / 514 (10.51%)	57 / 514 (11.09%)	
occurrences (all)	62	70	
Alopecia			
subjects affected / exposed	193 / 514 (37.55%)	182 / 514 (35.41%)	
occurrences (all)	198	185	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	28 / 514 (5.45%)	23 / 514 (4.47%)	
occurrences (all)	32	25	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	16 / 514 (3.11%)	35 / 514 (6.81%)	
occurrences (all)	17	37	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	46 / 514 (8.95%)	40 / 514 (7.78%)	
occurrences (all)	57	47	

Myalgia			
subjects affected / exposed	42 / 514 (8.17%)	49 / 514 (9.53%)	
occurrences (all)	50	55	
Bone pain			
subjects affected / exposed	45 / 514 (8.75%)	44 / 514 (8.56%)	
occurrences (all)	51	47	
Back pain			
subjects affected / exposed	101 / 514 (19.65%)	91 / 514 (17.70%)	
occurrences (all)	117	105	
Arthralgia			
subjects affected / exposed	99 / 514 (19.26%)	86 / 514 (16.73%)	
occurrences (all)	122	125	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	33 / 514 (6.42%)	36 / 514 (7.00%)	
occurrences (all)	38	48	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	15 / 514 (2.92%)	27 / 514 (5.25%)	
occurrences (all)	20	37	
Hyperglycaemia			
subjects affected / exposed	54 / 514 (10.51%)	47 / 514 (9.14%)	
occurrences (all)	67	54	
Decreased appetite			
subjects affected / exposed	98 / 514 (19.07%)	107 / 514 (20.82%)	
occurrences (all)	126	145	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2019	Amendment 1 included corrections to the Schedule of Activities, Objectives, and Appendices, and minor edits throughout.
10 February 2020	Amendment 2 included changes to eligibility criteria to align with latest standard of care (SOC) (NHAs given prior to mCRPC), and updates to stratification criteria to reflect this change.
17 September 2020	Amendment 3 included addition of an extension portion in China to allow for the required exposure and number of events to investigate efficacy and safety in participants enrolled in China.
21 July 2021	Amendment 4 included an update to the dose modification and toxicity management guidelines for irAEs.
14 January 2022	Amendment 5 included addition of the TEA survey to document the investigator's choice to recruit participants for the MK-3475-921 study rather than using other available treatment options.
08 November 2022	Amendment 6 included information on the study having achieved its prespecified scientific objective to evaluate the combination of pembrolizumab and docetaxel in this setting, and the study being closed as a result of having completed its final analysis. It also included language to state that upon study completion, participants are discontinued from the study and may be enrolled in a pembrolizumab extension study, if available.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported