Clinical trial results:
A Phase III, Randomized, Multi-Center, Double-Blind, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination With and following Chemoradiotherapy Compared to Chemoradiotherapy Alone for Treatment in Women With Locally Advanced Cervical Cancer (CALLA)

Summary

EudraCT number	2018-002872-42
Trial protocol	HU PL
Global end of trial date	03 July 2023

Results information

Result version number	v1 (current)
This version publication date	19 July 2024
First version publication date	19 July 2024

Trial information

Trial identification

Sponsor protocol code	D9100C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03830866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Clinical Study Information Center
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, 1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca Clinical Study Information Center, 1 8772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 July 2023
Global end of trial reached?	Yes
Global end of trial date	03 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of durvalumab + SoC CCRT compared with placebo + SoC CCRT in terms of PFS as assessed by investigator tumor assessments and histopathologic confirmation of local tumor progression.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 58
Country: Number of subjects enrolled	Hungary: 49
Country: Number of subjects enrolled	Korea, Republic of: 41
Country: Number of subjects enrolled	United States: 26
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Mexico: 114
Country: Number of subjects enrolled	China: 105
Country: Number of subjects enrolled	Peru: 104
Country: Number of subjects enrolled	Brazil: 78
Country: Number of subjects enrolled	Chile: 45
Country: Number of subjects enrolled	Russian Federation: 37
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	India: 31
Country: Number of subjects enrolled	Philippines: 23
Country: Number of subjects enrolled	South Africa: 2
Worldwide total number of subjects	770
EEA total number of subjects	69

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)	686
From 65 to 84 years	84
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Consenting subjects were assessed to ensure they met eligibility criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Durvalumab + SoC CCRT

Arm description:

Durvalumab 1500mg IV infusion every 4 weeks plus Standard of Care (SoC) concurrent chemoradiotherapy (CCRT) (chemotherapy for 5 weeks plus external beam radiotherapy and brachytherapy)

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	MEDI4736
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1500 mg IV q4w

Investigational medicinal product name	Standard of Care (SOC)
Investigational medicinal product code	Carboplatin
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV (Sourced locally by site)

Investigational medicinal product name	Standard of Care (SOC)
Investigational medicinal product code	Cisplatin
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV (Sourced locally by site)

Arm title	Placebo + SoC CCRT

Arm description:

Placebo IV infusion every 4 weeks plus Standard of Care (SoC) concurrent chemoradiotherapy (CCRT) (chemotherapy for 5 weeks plus external beam radiotherapy and brachytherapy)

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline solution
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: Dosing to match durvalumab	
Investigational medicinal product name	Standard of Care (SOC)
Investigational medicinal product code	Carboplatin
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: IV (Sourced locally by site)	
Investigational medicinal product name	Standard of Care (SOC)
Investigational medicinal product code	Cisplatin
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use
Dosage and administration details: IV (Sourced locally by site)	

Number of subjects in period 1	Durvalumab + SoC CCRT	Placebo + SoC CCRT
Started	385	385
Completed	268	249
Not completed	117	136
Adverse event, serious fatal	90	111
Consent withdrawn by subject	19	16
Not eligible due to additional cancer diagnosis	-	1
Unknown	1	1
Lost to follow-up	7	7

Baseline characteristics

Reporting groups	
Reporting group title	Durvalumab + SoC CCRT
Reporting group description:	
Durvalumab 1500mg IV infusion every 4 weeks plus Standard of Care (SoC) concurrent chemoradiotherapy (CCRT) (chemotherapy for 5 weeks plus external beam radiotherapy and brachytherapy)	
Reporting group title	Placebo + SoC CCRT
Reporting group description:	
Placebo IV infusion every 4 weeks plus Standard of Care (SoC) concurrent chemoradiotherapy (CCRT) (chemotherapy for 5 weeks plus external beam radiotherapy and brachytherapy)	

Reporting group values	Durvalumab + SoC CCRT	Placebo + SoC CCRT	Total
Number of subjects	385	385	770
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)	341	345	686
From 65-84 years	44	40	84
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	49.6	48.8	
standard deviation	± 11.74	± 11.67	-
Sex: Female, Male Units:			
Female	385	385	770
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	130	125	255
Black or African American	10	12	22
Asian	152	148	300
American Indian or Alaska Native	47	56	103
Other	46	44	90

End points

End points reporting groups

Reporting group title	Durvalumab + SoC CCRT
Reporting group description:	
Durvalumab 1500mg IV infusion every 4 weeks plus Standard of Care (SoC) concurrent chemoradiotherapy (CCRT) (chemotherapy for 5 weeks plus external beam radiotherapy and brachytherapy)	
Reporting group title	Placebo + SoC CCRT
Reporting group description:	
Placebo IV infusion every 4 weeks plus Standard of Care (SoC) concurrent chemoradiotherapy (CCRT) (chemotherapy for 5 weeks plus external beam radiotherapy and brachytherapy)	

Primary: Progression-free survival (PFS) based on the investigator assessment according to RECIST 1.1 or histopathologic confirmation of local tumour progression

End point title	Progression-free survival (PFS) based on the investigator assessment according to RECIST 1.1 or histopathologic confirmation of local tumour progression
End point description:	
PFS defined as time from date of randomisation until date of tumour progression or death by any cause, regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to progression	
End point type	Primary
End point timeframe:	
Tumor assessments start 20 weeks after randomisation then every 12 weeks up to 164 weeks, then every 24 weeks until date of RECIST1.1 defined radiological progression. Assessed up to date of DCO (20-Jan-2022) to a maximum of 32.6 months	

End point values	Durvalumab + SoC CCRT	Placebo + SoC CCRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	385		
Units: Months				
median (confidence interval 95%)	999999999 (999999999 to 999999999)	999999999 (999999999 to 999999999)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Durvalumab + SoC CCRT v Placebo + SoC CCRT

Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.174
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.08

Secondary: Overall Survival (count)

End point title	Overall Survival (count)

End point description:

Number of Participants with Overall Survival (OS) where OS was defined as the time from the date of randomisation until death by any cause

End point type	Secondary

End point timeframe:

Time from date of randomisation until date of death by any cause, assessed up to the data cut-off date (3rd July 2023), assessed up to a maximum of 51.7 months

End point values	Durvalumab + SoC CCRT	Placebo + SoC CCRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	385		
Units: Participants				
Died	91	112		
Censored includes w/d consent & lost to follow up	294	273		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) based on the investigator assessment according to RECIST 1.1 or histopathologic confirmation of local tumour progression, PD-L1 Expression >= 1%

End point title	Progression-free survival (PFS) based on the investigator assessment according to RECIST 1.1 or histopathologic confirmation of local tumour progression, PD-L1 Expression >= 1%

End point description:

PFS defined as time from date of randomisation until date of tumour progression or death by any cause, regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to progression

End point type	Secondary

End point timeframe:

Tumor assessments start 20 weeks after randomisation then every 12 weeks up to 164 weeks, then every 24 weeks until date of RECIST1.1 defined radiological progression. Assessed up to date of DCO (20-Jan-2022) to a maximum of 32.6 months

End point values	Durvalumab + SoC CCRT	Placebo + SoC CCRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	385		
Units: Months				
median (confidence interval 95%)	999999999 (999999999 to 999999999)	999999999 (26.9 to 999999999)		

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Durvalumab + SoC CCRT v Placebo + SoC CCRT
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.203
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.1

Secondary: Overall Survival (duration)

End point title	Overall Survival (duration)

End point description:

Time from the date of randomisation until death by any cause

End point type	Secondary

End point timeframe:

Time from date of randomisation until date of death by any cause, assessed up to the data cut-off date (3rd July 2023), assessed up to a maximum of 51.7 months

End point values	Durvalumab + SoC CCRT	Placebo + SoC CCRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	385		
Units: Months				
median (confidence interval 95%)	999999999 (999999999 to 999999999)	999999999 (999999999 to 999999999)		

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Durvalumab + SoC CCRT v Placebo + SoC CCRT
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.091
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.04

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Percentage of evaluable patients with an Investigator-assessed visit response of complete response (CR) or partial response (PR). CR defined as disappearance of all target and non-target lesions and no new lesions. PR defined as >= 30% decrease in the sum of diameters of target lesions (compared to baseline) and no new non-target lesion

End point type	Secondary

End point timeframe:

Tumor assessments start 20 weeks after randomisation then every 12 weeks up to 164 weeks, then every 24 weeks until date of RECIST1.1 defined radiological progression. Assessed up to date of DCO (20-Jan-2022) to a maximum of 32.6 months

End point values	Durvalumab + SoC CCRT	Placebo + SoC CCRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	385		
Units: Percentage of Participants				
number (not applicable)	82.6	80.5		

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Durvalumab + SoC CCRT v Placebo + SoC CCRT
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.465
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.794
upper limit	1.657

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

Percentage of evaluable patients with an overall visit response of Complete Response (disappearance of all target and non-target lesions)

End point type	Secondary

End point timeframe:

Tumor assessments start 20 weeks after randomisation then every 12 weeks up to 164 weeks, then every 24 weeks until date of RECIST1.1 defined radiological progression. Assessed up to date of DCO (20-Jan-2022) to a maximum of 32.6 months

End point values	Durvalumab + SoC CCRT	Placebo + SoC CCRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	385		
Units: Percentage of Participants				
number (not applicable)	42.9	40.3		

Statistical analyses

Statistical analysis title	Secondary analysis
Comparison groups	Durvalumab + SoC CCRT v Placebo + SoC CCRT
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.469
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.833
upper limit	1.487

Secondary: Duration of Response (DoR) in patients with Complete Response (CR)

End point title	Duration of Response (DoR) in patients with Complete Response (CR)

End point description:

Time from date of first documented CR until date of documented progression or death in the absence of progression. For patients who did not progress their DoR was their Progression-free survival censoring time

End point type	Secondary

End point timeframe:

Tumor assessments start 20 weeks after randomisation then every 12 weeks up to 164 weeks, then every 24 weeks until date of RECIST1.1 defined radiological progression. Assessed up to date of DCO (20-Jan-2022) to a maximum of 32.6 months

End point values	Durvalumab + SoC CCRT	Placebo + SoC CCRT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	385		
Units: Months				
median (inter-quartile range (Q1-Q3))	999999999 (999999999 to 999999999)	999999999 (999999999 to 999999999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent throughout the treatment period (median duration of 656 & 532 days for durvalumab & placebo respectively) up to & including 90-day safety follow-up period after the last dose of study treatment, up to a maximum of 53 months.

Adverse event reporting additional description:

There were 385 subjects randomised to each of Durva + SoC CCRT and Placebo + SoC CCRT respectively (Full Analysis Set), however 1 of the subjects allocated to Placebo + SoC CCRT did not receive treatment, resulting in 384 in the Safety Analysis Set. Causally related AEs are those that are possibly related to Durvalumab/Placebo only.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Placebo + SoC CCRT

Reporting group description:

Description (Arm-group)

Reporting group title	Durva + SoC CCRT

Reporting group description:

Description (Arm-group)

Serious adverse events	Placebo + SoC CCRT	Durva + SoC CCRT	
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 384 (23.44%)	113 / 385 (29.35%)	
number of deaths (all causes)	112	91	
number of deaths resulting from adverse events	5	14	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			

subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected neoplasm			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer in situ			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory pseudotumour			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Venous thrombosis limb			
subjects affected / exposed	2 / 384 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accelerated hypertension			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (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	0 / 384 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 384 (0.26%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix haemorrhage uterine			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	5 / 384 (1.30%)	7 / 385 (1.82%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	

Vaginal fistula			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			
subjects affected / exposed	2 / 384 (0.52%)	4 / 385 (1.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	4 / 384 (1.04%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute psychosis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 384 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram q wave abnormal			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Full blood count decreased			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (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 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Platelet count decreased			
subjects affected / exposed	3 / 384 (0.78%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 384 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Radiation proctitis			
subjects affected / exposed	2 / 384 (0.52%)	6 / 385 (1.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine perforation			
subjects affected / exposed	2 / 384 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis radiation			
subjects affected / exposed	1 / 384 (0.26%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystitis radiation			
subjects affected / exposed	4 / 384 (1.04%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 384 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebral infarction			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	20 / 384 (5.21%)	20 / 385 (5.19%)	
occurrences causally related to treatment / all	0 / 20	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	1 / 384 (0.26%)	5 / 385 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	2 / 384 (0.52%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 384 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 384 (0.52%)	6 / 385 (1.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal disorder			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 384 (0.26%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 384 (0.52%)	4 / 385 (1.04%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 384 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal ulcer			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
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	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 384 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	2 / 384 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
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	1 / 384 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 384 (0.26%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			

subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Telangiectasia			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exfoliative rash			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatomyositis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 384 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	3 / 384 (0.78%)	6 / 385 (1.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric fistula			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 384 (0.00%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 384 (0.26%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urogenital fistula			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorder			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (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	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device related infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (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 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19			
subjects affected / exposed	1 / 384 (0.26%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometritis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis c			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			

subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	11 / 384 (2.86%)	16 / 385 (4.16%)	
occurrences causally related to treatment / all	0 / 15	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ureteritis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			

subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 384 (0.26%)	3 / 385 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Salpingitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 384 (0.52%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 384 (0.52%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 384 (1.04%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pelvic infection			

subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine infection			
subjects affected / exposed	1 / 384 (0.26%)	0 / 385 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 384 (0.26%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 384 (1.04%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			

subjects affected / exposed	0 / 384 (0.00%)	2 / 385 (0.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 384 (0.00%)	1 / 385 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + SoC CCRT	Durva + SoC CCRT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	368 / 384 (95.83%)	373 / 385 (96.88%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	21 / 384 (5.47%)	28 / 385 (7.27%)	
occurrences (all)	24	31	
Hypertension			
subjects affected / exposed	24 / 384 (6.25%)	16 / 385 (4.16%)	
occurrences (all)	31	25	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	32 / 384 (8.33%)	35 / 385 (9.09%)	
occurrences (all)	37	51	
Asthenia			
subjects affected / exposed	35 / 384 (9.11%)	34 / 385 (8.83%)	
occurrences (all)	43	45	
Fatigue			
subjects affected / exposed	70 / 384 (18.23%)	52 / 385 (13.51%)	
occurrences (all)	79	55	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	37 / 384 (9.64%)	40 / 385 (10.39%)	
occurrences (all)	41	48	
Vaginal discharge			

subjects affected / exposed	28 / 384 (7.29%)	30 / 385 (7.79%)	
occurrences (all)	31	37	
Vaginal haemorrhage			
subjects affected / exposed	29 / 384 (7.55%)	24 / 385 (6.23%)	
occurrences (all)	33	28	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	33 / 384 (8.59%)	41 / 385 (10.65%)	
occurrences (all)	34	47	
Investigations			
Blood creatinine increased			
subjects affected / exposed	23 / 384 (5.99%)	31 / 385 (8.05%)	
occurrences (all)	30	48	
Gamma-glutamyltransferase increased			
subjects affected / exposed	28 / 384 (7.29%)	30 / 385 (7.79%)	
occurrences (all)	37	41	
Aspartate aminotransferase increased			
subjects affected / exposed	30 / 384 (7.81%)	34 / 385 (8.83%)	
occurrences (all)	38	56	
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 384 (3.39%)	21 / 385 (5.45%)	
occurrences (all)	17	30	
Platelet count decreased			
subjects affected / exposed	62 / 384 (16.15%)	48 / 385 (12.47%)	
occurrences (all)	107	81	
Neutrophil count decreased			
subjects affected / exposed	85 / 384 (22.14%)	74 / 385 (19.22%)	
occurrences (all)	221	216	
Lymphocyte count decreased			
subjects affected / exposed	34 / 384 (8.85%)	18 / 385 (4.68%)	
occurrences (all)	47	29	
Weight decreased			
subjects affected / exposed	42 / 384 (10.94%)	43 / 385 (11.17%)	
occurrences (all)	53	46	
White blood cell count decreased			

subjects affected / exposed	85 / 384 (22.14%)	71 / 385 (18.44%)	
occurrences (all)	340	296	
Alanine aminotransferase increased			
subjects affected / exposed	37 / 384 (9.64%)	43 / 385 (11.17%)	
occurrences (all)	48	64	
Injury, poisoning and procedural complications			
Gastroenteritis radiation			
subjects affected / exposed	10 / 384 (2.60%)	20 / 385 (5.19%)	
occurrences (all)	10	21	
Radiation skin injury			
subjects affected / exposed	27 / 384 (7.03%)	17 / 385 (4.42%)	
occurrences (all)	27	18	
Radiation proctitis			
subjects affected / exposed	26 / 384 (6.77%)	25 / 385 (6.49%)	
occurrences (all)	26	27	
Nervous system disorders			
Headache			
subjects affected / exposed	43 / 384 (11.20%)	42 / 385 (10.91%)	
occurrences (all)	51	55	
Dizziness			
subjects affected / exposed	20 / 384 (5.21%)	19 / 385 (4.94%)	
occurrences (all)	25	24	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	28 / 384 (7.29%)	38 / 385 (9.87%)	
occurrences (all)	38	46	
Lymphopenia			
subjects affected / exposed	29 / 384 (7.55%)	39 / 385 (10.13%)	
occurrences (all)	51	59	
Leukopenia			
subjects affected / exposed	58 / 384 (15.10%)	59 / 385 (15.32%)	
occurrences (all)	120	100	
Anaemia			
subjects affected / exposed	200 / 384 (52.08%)	209 / 385 (54.29%)	
occurrences (all)	322	315	
Neutropenia			

subjects affected / exposed	55 / 384 (14.32%)	74 / 385 (19.22%)	
occurrences (all)	100	120	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	11 / 384 (2.86%)	20 / 385 (5.19%)	
occurrences (all)	13	21	
Abdominal pain			
subjects affected / exposed	54 / 384 (14.06%)	50 / 385 (12.99%)	
occurrences (all)	68	71	
Abdominal pain upper			
subjects affected / exposed	20 / 384 (5.21%)	30 / 385 (7.79%)	
occurrences (all)	23	31	
Constipation			
subjects affected / exposed	87 / 384 (22.66%)	97 / 385 (25.19%)	
occurrences (all)	106	119	
Diarrhoea			
subjects affected / exposed	190 / 384 (49.48%)	177 / 385 (45.97%)	
occurrences (all)	289	257	
Haemorrhoids			
subjects affected / exposed	23 / 384 (5.99%)	14 / 385 (3.64%)	
occurrences (all)	24	14	
Nausea			
subjects affected / exposed	202 / 384 (52.60%)	213 / 385 (55.32%)	
occurrences (all)	293	289	
Vomiting			
subjects affected / exposed	107 / 384 (27.86%)	105 / 385 (27.27%)	
occurrences (all)	202	194	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	70 / 384 (18.23%)	61 / 385 (15.84%)	
occurrences (all)	80	74	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	12 / 384 (3.13%)	26 / 385 (6.75%)	
occurrences (all)	13	27	
Hypothyroidism			

subjects affected / exposed	21 / 384 (5.47%)	60 / 385 (15.58%)	
occurrences (all)	21	68	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	14 / 384 (3.65%)	26 / 385 (6.75%)	
occurrences (all)	18	29	
Back pain			
subjects affected / exposed	43 / 384 (11.20%)	40 / 385 (10.39%)	
occurrences (all)	45	47	
Arthralgia			
subjects affected / exposed	42 / 384 (10.94%)	44 / 385 (11.43%)	
occurrences (all)	49	51	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	4 / 384 (1.04%)	22 / 385 (5.71%)	
occurrences (all)	5	24	
Cystitis			
subjects affected / exposed	19 / 384 (4.95%)	25 / 385 (6.49%)	
occurrences (all)	21	28	
Covid-19			
subjects affected / exposed	40 / 384 (10.42%)	29 / 385 (7.53%)	
occurrences (all)	46	29	
Urinary tract infection			
subjects affected / exposed	92 / 384 (23.96%)	90 / 385 (23.38%)	
occurrences (all)	124	123	
Upper respiratory tract infection			
subjects affected / exposed	14 / 384 (3.65%)	26 / 385 (6.75%)	
occurrences (all)	19	27	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	64 / 384 (16.67%)	89 / 385 (23.12%)	
occurrences (all)	74	103	
Hyperglycaemia			
subjects affected / exposed	19 / 384 (4.95%)	26 / 385 (6.75%)	
occurrences (all)	23	28	
Hyponatraemia			

subjects affected / exposed	23 / 384 (5.99%)	29 / 385 (7.53%)	
occurrences (all)	29	40	
Hypomagnesaemia			
subjects affected / exposed	38 / 384 (9.90%)	40 / 385 (10.39%)	
occurrences (all)	61	52	
Hypokalaemia			
subjects affected / exposed	46 / 384 (11.98%)	44 / 385 (11.43%)	
occurrences (all)	74	63	
Hypoalbuminaemia			
subjects affected / exposed	25 / 384 (6.51%)	24 / 385 (6.23%)	
occurrences (all)	34	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2018	Version 1.0. Initial creation
09 September 2019	Version 2. PFS analysis at 3 years moved from exploratory objective to secondary objective. Clarified that duration of response in patients with a complete response endpoint is measured from the date of first detection of CR as determined at the 20-week assessment.
29 May 2020	Version 3. Removal of Carboplatin. To ensure appropriate balance between patients treated with cisplatin and carboplatin as the radiosensitizer across regions in the ongoing study, no further use of carboplatin as the radiosensitizer will be allowed in this study.
11 March 2021	Version 4. Removal of interim analyses for PFS and removal of first two interim analyses for OS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported