Clinical trial results:
A Phase II, Open-Label, Multi-Centre, International Safety Study of Durvalumab Following Sequential Chemotherapy and Radiation Therapy in Patients with Stage III, Unresectable Non-Small Cell Lung Cancer (PACIFIC 6)

Summary

EudraCT number	2018-002220-16
Trial protocol	GB FR ES DE IT
Global end of trial date	21 April 2023

Results information

Result version number	v2 (current)
This version publication date	30 June 2024
First version publication date	05 May 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D4194C00006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03693300
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, 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	16 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability profile of durvalumab (MEDI4736) as defined by Grade 3 and Grade 4 Treatment-related adverse events (TRAEs) within 6 months from the initiation of durvalumab (MEDI4736) treatment.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics. Written informed consent was obtained before the patient was enrolled in the study, along with the date the written consent was obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 April 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	United States: 2
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	France: 16
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Spain: 30
Worldwide total number of subjects	117
EEA total number of subjects	103

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)	40
From 65 to 84 years	76
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 16 April 2019 to 21 April 2023 at 25 sites in the United States of America (USA), France, Germany, Italy, Spain, and the United Kingdom.

Pre-assignment

Screening details:

Patients who met all the inclusion and none of the exclusion criteria were included in the study. The screening period was from Day -28 to Day -1. Informed consent form was signed prior to screening procedures.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Durvalumab ECOG PS 0 or 1

Arm description:

Patients received 1500 mg Durvalumab monotherapy via Intravenous (IV) infusion every 4 weeks (q4w).

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

Dosage and administration details:

Durvalumab 1500 mg was administered via IV infusion every 4 weeks.

Arm title	Durvalumab ECOG PS 2

Arm description:

Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.

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

Dosage and administration details:

Durvalumab 1500 mg was administered via IV infusion every 4 weeks.

Number of subjects in period 1	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2
Started	114	3
Completed	56	1
Not completed	58	2
Adverse event, serious fatal	50	2
Consent withdrawn by subject	6	-
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Durvalumab ECOG PS 0 or 1
Reporting group description:	
Patients received 1500 mg Durvalumab monotherapy via Intravenous (IV) infusion every 4 weeks (q4w).	
Reporting group title	Durvalumab ECOG PS 2
Reporting group description:	
Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.	

Reporting group values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2	Total
Number of subjects	114	3	117
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)	39	1	40
From 65-84 years	74	2	76
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	67.0	65.0	
standard deviation	± 8.46	± 12.00	-
Sex: Female, Male Units: participants			
Female	43	1	44
Male	71	2	73
Race/Ethnicity, Customized Units: Subjects			
White	101	3	104
Unknown	13	0	13
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	103	3	106
Unknown or Not Reported	10	0	10

End points

End points reporting groups

Reporting group title	Durvalumab ECOG PS 0 or 1
Reporting group description:	
Patients received 1500 mg Durvalumab monotherapy via Intravenous (IV) infusion every 4 weeks (q4w).	
Reporting group title	Durvalumab ECOG PS 2
Reporting group description:	
Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.	
Subject analysis set title	Durvalumab ECOG PS 0 or 1
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.	
Subject analysis set title	Durvalumab ECOG PS 2
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.	

Primary: Number of patients with Grade 3 and Grade 4 Treatment-related adverse events (TRAEs)

End point title	Number of patients with Grade 3 and Grade 4 Treatment-related adverse events (TRAEs)

End point description:

Safety and tolerability of Durvalumab as defined by Grade 3 and Grade 4 TRAEs following IV infusion administration was assessed.

The Subject Analysis set was added to report statistical analysis, and this is the only option available in order to accommodate reporting of statistical data for same cohorts.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full).

Category A: Any possibly related AEs of CTCAE Grade 3 or Grade 4
Category B: Any possibly related AEs of Grade 3 or Grade 4 with onset date within 6 months of the first dose

End point type	Primary

End point timeframe:

Up to 6 months

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	114	3	114	3
Units: Participants				
Category A	7	0	7	0
Category B	5	0	5	0

Statistical analyses

Statistical analysis title	Proportion and 95% CI for incidence of PRAEs
Statistical analysis description:	
Any possibly related adverse events of CTCAE Grade 3 or Grade 4. 95% CI were based on the Clopper-Pearson method.	
Comparison groups	Durvalumab ECOG PS 0 or 1 v Durvalumab ECOG PS 0 or 1
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Proportion (%)
Point estimate	6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	12.24

Statistical analysis title	Proportion and 95% CI for incidence of PRAEs
Statistical analysis description:	
Any possibly related AEs of Grade 3 or Grade 4 with onset date within 6 months of the first dose. 95% CI were based on the Clopper-Pearson method.	
Comparison groups	Durvalumab ECOG PS 2 v Durvalumab ECOG PS 2
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Proportion (%)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	70.76

Statistical analysis title	Proportion and 95% CI for incidence of PRAEs
Statistical analysis description:	
Any possibly related AEs of Grade 3 or Grade 4 with onset date within 6 months of the first dose. 95% CI were based on the Clopper-Pearson method.	
Comparison groups	Durvalumab ECOG PS 0 or 1 v Durvalumab ECOG PS 0 or 1
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Proportion (%)
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	9.94

Statistical analysis title	Proportion and 95% CI for incidence of PRAEs

Statistical analysis description:

Any possibly related adverse events of CTCAE Grade 3 or Grade 4.
95% CI were based on the Clopper-Pearson method.

Comparison groups	Durvalumab ECOG PS 2 v Durvalumab ECOG PS 2
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Proportion (%)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	70.76

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

The efficacy of Durvalumab (MEDI4736) treatment in terms of PFS. PFS was defined as the time from the first date of treatment until the date of objective disease progression based on Investigator's assessment according to RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from IP or receives another anticancer therapy prior to progression.

Here, arbitrary value 9999.9999 represent not calculated due to low number of events as well as low sample size.
The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full).

End point type	Secondary

End point timeframe:

From the first date of treatment until the date of objective disease progression or death (approximately upto 48 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	3		
Units: Months				
median (confidence interval 95%)	13.1 (7.36 to 19.91)	3.7 (1.81 to 9999.9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients alive

End point title	Percentage of patients alive

End point description:

Percentage of patients alive at 12 months, 24 months, and 36 months were estimated.

Here, arbitrary value 9999.9999 represent not calculated due to low number of events as well as low sample size.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full).

End point type	Secondary

End point timeframe:

From the first date of treatment until the date of objective disease progression or death (12 months, 24 months, and 36 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	3		
Units: Percentage of patient				
number (confidence interval 95%)				
Survival at 12 months	83.9 (75.73 to 89.57)	66.7 (5.41 to 94.52)		
Survival at 24 months	68.2 (58.54 to 76.00)	33.3 (0.90 to 77.41)		
Survival at 36 months	57.2 (46.94 to 66.20)	9999.9999 (9999.9999 to 9999.9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients progression-free at 12 months

End point title	Percentage of patients progression-free at 12 months

End point description:

The percentage of patients treated with Durvalumab who are progression-free was estimated. PFS12 according to RECIST 1.1 as assessed by the Investigator.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full).

End point type	Secondary

End point timeframe:

From the first date of treatment until the date of objective disease progression or death (upto 12 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	3		
Units: Percentage of patient				
number (confidence interval 95%)	51.1 (41.29 to 60.02)	33.3 (0.90 to 77.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

The efficacy of Durvalumab (MEDI4736) treatment in terms of OS were assessed. OS was defined as the time from the first date of treatment until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Here, arbitrary value 9999.9999 represent not calculated due to low number of events as well as low sample size.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full).

End point type	Secondary

End point timeframe:

From the first date of treatment until death due to any cause (approximately upto 48 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	3		
Units: Months				
median (confidence interval 95%)	39.0 (30.59 to 9999.9999)	12.3 (4.96 to 9999.9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) from onset of response

End point title	Duration of Response (DOR) from onset of response

End point description:

The efficacy of Durvalumab (MEDI4736) treatment in terms of DoR were assessed. DoR was defined as the time from the date of first documented response per RECIST1.1 until the first date of documented progression per RECIST1.1 or death in the absence of disease progression. If a patient did not progress following a response, then the patients' DoR was censored at the PFS censoring time.

Here, arbitrary value 9999.9999 represent not applicable - Not calculated due to insufficient number of events.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full). The patients with objective response were evaluated.

End point type	Secondary

End point timeframe:

From 8 weeks ±1 week after IP treatment initiation and continue q8w ±1 week through 52 weeks and q12w ±1 week until disease progression (approximately upto 48 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	0[1]		
Units: Weeks				
median (confidence interval 95%)	9999.9999 (9999.9999 to 9999.9999)	(to)		

Notes:

[1] - Not calculated due to insufficient number of events.

Statistical analyses

No statistical analyses for this end point

Secondary: Lung cancer mortality

End point title	Lung cancer mortality

End point description:

The efficacy of durvalumab (MEDI4736) treatment in terms of lung cancer mortality was assessed. Lung Cancer Mortality was defined as the time from the date of treatment start until death due to lung cancer. Any patient not known to have died due to lung cancer will be censored based on the last recorded date on which the patient was known to be alive or died due to reason other than lung cancer.

Here, arbitrary value 9999.9999 represent not applicable - Not calculated due to insufficient number of events.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full). Patients who had died due to causes related to non-small cell lung cancer were evaluated.

End point type	Secondary

End point timeframe:

From date of treatment start until death due to lung cancer (approximately upto 48 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	1		
Units: Months				
median (confidence interval 95%)	41.8 (36.50 to 9999.9999)	9999.9999 (4.96 to		

9999.9999)

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective response is complete response (CR), or partial response (PR) confirmed by a follow-up visit at least 4 weeks after. Both visits contributing to response should have occurred before any further anti-cancer therapy, in order for the patient to be considered a responder. Responses that occurred after the start of subsequent anti-cancer therapy were not included in the numerator. Response excluded unconfirmed response. Participants with unconfirmed responses include those whose CR, or PR don't have a confirmed response. These responses occur at any time during the study, recur after anti-cancer therapy, and these participants were missing for a follow-up visit 4 weeks after.
Here, arbitrary value 9999.9999 represent not applicable.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full).

End point type	Secondary

End point timeframe:

From 8 weeks ±1 week after investigational product (IP) treatment initiation and continue every 8 weeks (q8w) ±1 week through 52 weeks and every 12 weeks (q12w) ±1 week until disease progression (approximately upto 48 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	3		
Units: Participants				
Number of patients with response	24	0		
Number of patients with unconfirmed response	5	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse events (AEs), Serious adverse events (SAEs), Adverse event of special interests (AESIs), and Immune-mediated adverse event (imAEs)

End point title	Number of participants with Adverse events (AEs), Serious adverse events (SAEs), Adverse event of special interests (AESIs), and Immune-mediated adverse event (imAEs)

End point description:

The safety and tolerability profile of Durvalumab(MEDI4736) treatment, including all AEs were assessed.

The safety analysis set consisted of all patients who received at least one dose of IP (partial or in full). This include treatment emergent AEs only, ie. AEs occurred during screening period are NOT included.

End point type	Secondary

End point timeframe:

Until the final visit (upto 48 months)

End point values	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	3		
Units: Participants				
Any AE	108	3		
Any AE possibly related to treatment (PRT)	87	3		
Any AE of CTCAE Grade 3 or Grade 4	32	0		
Any AE of CTCAE Grade 3 or Grade 4 PRT	7	0		
Any AE with outcome of death	3	0		
Any AE with outcome of death PRT	1	0		
Any SAE (including events with outcome of death)	32	0		
Any SAE (inc. events with outcome of death) PRT	7	0		
Any AE leading to discontinuation of treatment	32	0		
Any AE leading to DOT PRT	19	0		
Any AE leading to treatment interruption	52	1		
Any AE leading to treatment interruption, PRT	24	1		
Any AESI/AEPI (inc. events with outcome of death)	86	3		
Any AESI/AEPI (events with outcome of death), PRT	73	2		
Any imAE	48	2		
Any imAE, PRT	43	2		
Any imAE as assessed by Investigator	64	1		
Any imAE as assessed by Investigator, PRT	64	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Upto 48 months	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0
Reporting groups	
Reporting group title	Durvalumab ECOG PS 0 or 1
Reporting group description: Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.	
Reporting group title	Durvalumab ECOG PS 2
Reporting group description: Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.	
Reporting group title	Durvalumab Total
Reporting group description: Patients received 1500 mg Durvalumab monotherapy via IV infusion q4w.	

Serious adverse events	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2	Durvalumab Total
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 114 (28.07%)	0 / 3 (0.00%)	23 / 117 (19.66%)
number of deaths (all causes)	50	2	52
number of deaths resulting from adverse events	3	0	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radiation pneumonitis			

subjects affected / exposed	2 / 114 (1.75%)	0 / 3 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 114 (1.75%)	0 / 3 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal cord compression			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 114 (1.75%)	0 / 3 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	5 / 114 (4.39%)	0 / 3 (0.00%)	5 / 117 (4.27%)
occurrences causally related to treatment / all	5 / 5	0 / 0	5 / 5
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Lung disorder			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal stenosis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoxia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			

subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 pneumonia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia legionella			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	5 / 114 (4.39%)	0 / 3 (0.00%)	5 / 117 (4.27%)
occurrences causally related to treatment / all	1 / 7	0 / 0	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 3 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Durvalumab ECOG PS 0 or 1	Durvalumab ECOG PS 2	Durvalumab Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 114 (92.98%)	3 / 3 (100.00%)	109 / 117 (93.16%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 114 (6.14%)	1 / 3 (33.33%)	8 / 117 (6.84%)
occurrences (all)	8	2	10
Hypotension			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Deep vein thrombosis			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	29 / 114 (25.44%)	2 / 3 (66.67%)	31 / 117 (26.50%)
occurrences (all)	40	2	42
Fatigue			
subjects affected / exposed	24 / 114 (21.05%)	0 / 3 (0.00%)	24 / 117 (20.51%)
occurrences (all)	35	0	35
Pyrexia			
subjects affected / exposed	22 / 114 (19.30%)	0 / 3 (0.00%)	22 / 117 (18.80%)
occurrences (all)	25	0	25
Non-cardiac chest pain			
subjects affected / exposed	15 / 114 (13.16%)	1 / 3 (33.33%)	16 / 117 (13.68%)
occurrences (all)	18	1	19
Oedema peripheral			
subjects affected / exposed	10 / 114 (8.77%)	0 / 3 (0.00%)	10 / 117 (8.55%)
occurrences (all)	10	0	10
Chills			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Chest discomfort			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Chest pain			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 114 (0.00%)	1 / 3 (33.33%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	16 / 114 (14.04%)	1 / 3 (33.33%)	17 / 117 (14.53%)
occurrences (all)	20	1	21
Dyspnoea			
subjects affected / exposed	27 / 114 (23.68%)	2 / 3 (66.67%)	29 / 117 (24.79%)
occurrences (all)	39	3	42
Cough			

subjects affected / exposed	43 / 114 (37.72%)	2 / 3 (66.67%)	45 / 117 (38.46%)
occurrences (all)	49	3	52
Productive cough			
subjects affected / exposed	10 / 114 (8.77%)	0 / 3 (0.00%)	10 / 117 (8.55%)
occurrences (all)	11	0	11
Haemoptysis			
subjects affected / exposed	6 / 114 (5.26%)	0 / 3 (0.00%)	6 / 117 (5.13%)
occurrences (all)	8	0	8
Oropharyngeal discomfort			
subjects affected / exposed	0 / 114 (0.00%)	1 / 3 (33.33%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Pneumothorax			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Pleuritic pain			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Oropharyngeal pain			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
Lung disorder			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Dyspnoea exertional			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 114 (6.14%)	0 / 3 (0.00%)	7 / 117 (5.98%)
occurrences (all)	7	0	7
Anxiety			
subjects affected / exposed	6 / 114 (5.26%)	0 / 3 (0.00%)	6 / 117 (5.13%)
occurrences (all)	6	0	6
Depressed mood			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4

Depression			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Investigations			
Blood creatinine increased			
subjects affected / exposed	8 / 114 (7.02%)	0 / 3 (0.00%)	8 / 117 (6.84%)
occurrences (all)	13	0	13
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 114 (6.14%)	0 / 3 (0.00%)	7 / 117 (5.98%)
occurrences (all)	9	0	9
Alanine aminotransferase increased			
subjects affected / exposed	6 / 114 (5.26%)	0 / 3 (0.00%)	6 / 117 (5.13%)
occurrences (all)	7	0	7
Weight decreased			
subjects affected / exposed	8 / 114 (7.02%)	0 / 3 (0.00%)	8 / 117 (6.84%)
occurrences (all)	8	0	8
Blood thyroid stimulating hormone increased			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Lipase increased			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	4	0	4
Blood glucose increased			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Platelet count decreased			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	4	0	4
Injury, poisoning and procedural			

complications			
Radiation pneumonitis			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 114 (14.91%)	1 / 3 (33.33%)	18 / 117 (15.38%)
occurrences (all)	18	1	19
Paraesthesia			
subjects affected / exposed	9 / 114 (7.89%)	0 / 3 (0.00%)	9 / 117 (7.69%)
occurrences (all)	9	0	9
Dizziness			
subjects affected / exposed	7 / 114 (6.14%)	0 / 3 (0.00%)	7 / 117 (5.98%)
occurrences (all)	13	0	13
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 114 (5.26%)	0 / 3 (0.00%)	6 / 117 (5.13%)
occurrences (all)	8	0	8
Lymphadenopathy			
subjects affected / exposed	0 / 114 (0.00%)	1 / 3 (33.33%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Lymphopenia			
subjects affected / exposed	6 / 114 (5.26%)	0 / 3 (0.00%)	6 / 117 (5.13%)
occurrences (all)	8	0	8
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	5	0	5
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	7 / 114 (6.14%)	0 / 3 (0.00%)	7 / 117 (5.98%)
occurrences (all)	7	0	7
Vomiting			
subjects affected / exposed	9 / 114 (7.89%)	0 / 3 (0.00%)	9 / 117 (7.69%)
occurrences (all)	9	0	9
Nausea			

subjects affected / exposed	17 / 114 (14.91%)	0 / 3 (0.00%)	17 / 117 (14.53%)
occurrences (all)	21	0	21
Diarrhoea			
subjects affected / exposed	24 / 114 (21.05%)	0 / 3 (0.00%)	24 / 117 (20.51%)
occurrences (all)	33	0	33
Constipation			
subjects affected / exposed	23 / 114 (20.18%)	0 / 3 (0.00%)	23 / 117 (19.66%)
occurrences (all)	24	0	24
Abdominal pain			
subjects affected / exposed	5 / 114 (4.39%)	0 / 3 (0.00%)	5 / 117 (4.27%)
occurrences (all)	5	0	5
Abdominal pain upper			
subjects affected / exposed	6 / 114 (5.26%)	0 / 3 (0.00%)	6 / 117 (5.13%)
occurrences (all)	6	0	6
Dyspepsia			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 114 (4.39%)	0 / 3 (0.00%)	5 / 117 (4.27%)
occurrences (all)	5	0	5
Noninfective gingivitis			
subjects affected / exposed	0 / 114 (0.00%)	1 / 3 (33.33%)	1 / 117 (0.85%)
occurrences (all)	0	1	1
Dysphagia			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	4	0	4
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	19 / 114 (16.67%)	2 / 3 (66.67%)	21 / 117 (17.95%)
occurrences (all)	21	3	24
Rash			
subjects affected / exposed	13 / 114 (11.40%)	1 / 3 (33.33%)	14 / 117 (11.97%)
occurrences (all)	17	1	18
Dry skin			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4

Erythema			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
Psoriasis			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	5	0	5
Rash pruritic			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Night sweats			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 114 (0.88%)	1 / 3 (33.33%)	2 / 117 (1.71%)
occurrences (all)	1	1	2
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	12 / 114 (10.53%)	0 / 3 (0.00%)	12 / 117 (10.26%)
occurrences (all)	12	0	12
Hypothyroidism			
subjects affected / exposed	15 / 114 (13.16%)	1 / 3 (33.33%)	16 / 117 (13.68%)
occurrences (all)	15	1	16
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 114 (19.30%)	1 / 3 (33.33%)	23 / 117 (19.66%)
occurrences (all)	28	2	30
Back pain			
subjects affected / exposed	17 / 114 (14.91%)	0 / 3 (0.00%)	17 / 117 (14.53%)
occurrences (all)	17	0	17
Neck pain			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	4	0	4
Pain in extremity			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	4	0	4

Myalgia			
subjects affected / exposed	5 / 114 (4.39%)	0 / 3 (0.00%)	5 / 117 (4.27%)
occurrences (all)	5	0	5
Musculoskeletal pain			
subjects affected / exposed	5 / 114 (4.39%)	0 / 3 (0.00%)	5 / 117 (4.27%)
occurrences (all)	5	0	5
Musculoskeletal chest pain			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	5	0	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 114 (8.77%)	0 / 3 (0.00%)	10 / 117 (8.55%)
occurrences (all)	12	0	12
Pneumonia			
subjects affected / exposed	8 / 114 (7.02%)	0 / 3 (0.00%)	8 / 117 (6.84%)
occurrences (all)	8	0	8
Conjunctivitis			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
Lower respiratory tract infection			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	6	0	6
Urinary tract infection			
subjects affected / exposed	5 / 114 (4.39%)	0 / 3 (0.00%)	5 / 117 (4.27%)
occurrences (all)	5	0	5
Rhinitis			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Oral candidiasis			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4
COVID-19			
subjects affected / exposed	7 / 114 (6.14%)	0 / 3 (0.00%)	7 / 117 (5.98%)
occurrences (all)	7	0	7
Metabolism and nutrition disorders			

Hypomagnesaemia			
subjects affected / exposed	6 / 114 (5.26%)	0 / 3 (0.00%)	6 / 117 (5.13%)
occurrences (all)	6	0	6
Hyperglycaemia			
subjects affected / exposed	7 / 114 (6.14%)	1 / 3 (33.33%)	8 / 117 (6.84%)
occurrences (all)	8	1	9
Decreased appetite			
subjects affected / exposed	14 / 114 (12.28%)	1 / 3 (33.33%)	15 / 117 (12.82%)
occurrences (all)	14	2	16
Hyperuricaemia			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	3	0	3
Hypercalcaemia			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	4	0	4
Hyperkalaemia			
subjects affected / exposed	3 / 114 (2.63%)	0 / 3 (0.00%)	3 / 117 (2.56%)
occurrences (all)	6	0	6
Hypokalaemia			
subjects affected / exposed	4 / 114 (3.51%)	0 / 3 (0.00%)	4 / 117 (3.42%)
occurrences (all)	4	0	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2019	Section 5.1 (Inclusion criteria): Reference to hepatic metastasis alanine aminotransferase and aspartate aminotransferase limits for patients with hepatic metastases has been removed as patients are required to have non-metastatic disease. Section 5.1 and 5.2 (Eligibility criteria): Eligibility criteria have been updated to allow gemcitabine in combination with cisplatin or carboplatin as a prior sCRT treatment, provided there is no overlap between chemotherapy and radiation. Section 8.2.1 (Haematology safety laboratory assessments): Clarification of language related to coagulation testing at baseline on Day 1. Section 8.4.5.1 (Toxicity management related to durvalumab) and Appendix G: Section has been updated to reflect that Toxicity Management Guidelines (TMGs) are now provided as an Annex to the Protocol. Appendix G has been removed.
20 April 2020	Section 1.1 (Synopsis), Section 1.2, Table 1 (SoA), Section 1.3 (Figure 1), Section 4.1 (Overall Design), Section 4.1 (Overall Design) Figure 2, Section 4.2.5 (Timing of treatment with durvalumab (MEDI4736) relative to sequential chemoradiation therapy), Section 5.1 (Inclusion Criteria), Section 9.2 (Sample Size Determination) Table 13: The time window from end of sCRT to first dose of IP was extended from 28 to 42 days. Section 1.2, Table 1, Footnote l (SoA): The frequency of on study pregnancy testing was changed from “every 4 weeks” to “prior to every dosing visit (within 3 calendar days prior to dosing in line with other laboratory tests)”. Section 5.1 (Inclusion Criterion 7): Inclusion criterion 7 was amended to supplement guidance on acceptable baseline imaging. It was added that assessment of tumour response should be performed based on the latest scan performed per physician assessment/criteria). If the patient has an intermediate scan between chemotherapy and radiotherapy, this scan should be used as baseline scan provided it fulfils the RECIST-defined CT imaging acquisition parameters. Section 5.2 (Exclusion Criterion 11, option (a)): It was added to exclusion criterion 11 that patients with ≥Grade 2 lymphopenia will be evaluated on a case-by-case basis after consultation with the Study Physician. Section 8.2.2 (Physical Examination): Clarification was made that targeted physical examinations during the treatment cycles are not expected in asymptomatic patients. Section 8.2.3 (Vital Signs): Clarification that respiratory rate and temperature measurements are part of the vital signs assessments. Section 9.2 (Sample Size Determination): The sample size per cohort was changed: WHO/ECOG PS 0 to 1 cohort from 120 to 100-120 patients and WHO/ECOG PS 2 cohort from 30 to up to 30, depending on recruitment.

06 July 2021	Section 1.1 (Synopsis), Section 3 (Study objectives), Table 3 footnote: It was clarified that TRAEs and PRAEs are used interchangeably and PRAEs will be reported in the SAP, Tables, Figures, and Listings, and CSR Section 1.1 (Synopsis, Treatments and treatment duration), Section 4.1 (Overall design, Figure 2), and Section 6.1.2 (Dose and treatment regimens): It was clarified that treatment for up to a maximum of 24 months is referring to a maximum of 24 months from Cycle 1 Day 1. Section 4.1 (Overall design, Investigational product, dosage and mode of administration): It was clarified that treatment is for a maximum of 24 months from Cycle 1 Day 1. Section 6.1.1 (Investigational product, Preparation of durvalumab (MEDI4736) doses for administration with an IV bag) and Section 8.2.3 (Vital signs): A time window of ±10 minutes for the durvalumab infusion time was added based on latest AstraZeneca durvalumab protocol template. Section 6.1.3 (Treatment after the end of the study, Treatment after final overall survival data cut-off): The misleading sentence that no OS data will be recorded in the study database after DCO was deleted and it was clarified that in this section the DCO is referring to the final DCO Section 8.3.13 (Safety data to be collected following the final data cut-off of the study): It was clarified that in this section the DCO is referring to the final DCO. Section 8.4.1 (Reporting of serious adverse events): The guidance on how to proceed if the WBDC system is unavailable was updated to match the safety handling plan. Section 8.4.5.1 (Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab): The reference to the website containing the current Dosing Modification and Toxicity Management Guidelines was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported