Clinical trial results:
A Phase II, Multi-Center, Single-Arm, Global Study of MEDI4736 Monotherapy in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Summary

EudraCT number	2014-003295-23
Trial protocol	GB BE DE HU ES CZ
Global end of trial date	06 July 2020

Results information

Result version number	v1 (current)
This version publication date	27 September 2020
First version publication date	27 September 2020

Trial information

Trial identification

Sponsor protocol code	D4193C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02207530
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca LP
Sponsor organisation address	1 MedImmune Way, Gaithersburg, United States, MD 20878
Public contact	Jean Fan, MD, Global Clinical Lead, AstraZeneca LP, +1 13013985080, jean.fan@astrazeneca.com
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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	31 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of durvalumab monotherapy in terms of objective response rate (ORR)

Protection of trial subjects:

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 39
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Georgia: 2
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Malaysia: 1
Worldwide total number of subjects	112
EEA total number of subjects	59

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)	83
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

110 sites in 14 countries enrolled and screened patients. The study was conducted and managed by PRA, a contract research organization.

Pre-assignment

Screening details:

Screening took place between Day -28 and Day -1. Informed consent, study procedures and laboratory assessments (including PD-L1 testing) were undertaken over the course of 1 or more visits.

Period 1

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

Arms

Arm title	MEDI4736

Arm description:

MEDI4736 monotherapy: Durvalumab was provided at a dose of 10 mg/kg using an intravenous solution every 2 weeks until 12 months, disease progression, toxicity, or patient decision to stop therapy

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

Dosage and administration details:

Patients will receive 10 mg/kg MEDI4736 via intravenous infusion every 2 weeks (q2w) beginning on Day 0 for 12 months or until confirmed progression of disease

Number of subjects in period 1	MEDI4736
Started	112
Completed	21
Not completed	91
Patient decision to stop study treatment	5
Adverse event, non-fatal	8
Worsening condition under investigation	78

Baseline characteristics

Reporting groups	
Reporting group title	MEDI4736
Reporting group description:	
MEDI4736 monotherapy: Durvalumab was provided at a dose of 10 mg/kg using an intravenous solution every 2 weeks until 12 months, disease progression, toxicity, or patient decision to stop therapy	

Reporting group values	MEDI4736	Total	
Number of subjects	112	112	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	83	83	
>=65 years	29	29	
Age Continuous Units: Years			
median	60.0		
full range (min-max)	24 to 84	-	
Sex: Female, Male Units: Subjects			
Female	32	32	
Male	80	80	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	4	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	5	5	
White	100	100	
More than one race	0	0	
Unknown or Not Reported	3	3	
Smoking/ Nicotine status Units: Subjects			
>10 Pack years|	49	49	
<=10 pack years|	53	53	
Unknown/ Not reported|	10	10	
Nicotine Use Units: Subjects			
Current|	10	10	
Former|	59	59	
Never|	43	43	
HPV status			
99 subjects were analyzed for HPV status			
Units: Subjects			
Positive|	34	34	
Negative|	65	65	
Unknown/ Not reported|	13	13	

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	109	109	
Unknown/ Not Reported	2	2	
WHO/ECOG performance status Units: Subjects			
(0) Normal activity|	34	34	
(1) Restricted activity|	77	77	
Missing|	1	1	
Programmed Cell Death Ligand 1 Status Units: Subjects			
Positive	112	112	
Height Units: cm			
arithmetic mean	171.7		
standard deviation	± 8.96	-	
Weight Units: kg			
arithmetic mean	69.7		
standard deviation	± 16.36	-	
Body Mass Index Units: kg/ m^2			
arithmetic mean	23.44		
standard deviation	± 4.514	-	

End points

End points reporting groups

Reporting group title	MEDI4736

Reporting group description:

MEDI4736 monotherapy: Durvalumab was provided at a dose of 10 mg/kg using an intravenous solution every 2 weeks until 12 months, disease progression, toxicity, or patient decision to stop therapy

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

Objective response rate (per RECIST 1.1 as assessed by blinded independent central review [BICR]) is defined as the number (%) of patients with a confirmed complete response or confirmed partial response and will be based on all treated patients who are PD-L1-positive with measurable disease at baseline per BICR. Response Evaluation Criteria in Solid Tumors [RECIST] 1.1. criteria are: Complete response [CR] = disappearance of all target lesions since baseline; and partial response [PR] = at least a 30% decrease in the sum of the diameters of target lesions. Confidence interval values of 0 to 99999 were used where results were not applicable.

End point type	Primary

End point timeframe:

12 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: 'No additional statistical analysis was planned for this endpoint.

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: % of participants				
number (confidence interval 95%)				
Overall|	16.2 (9.9 to 24.41)			
Smoking/nicotine status >10 pack years|	14.6 (6.07 to 27.76)			
Smoking/nicotine status <=10 pack years|	18.9 (9.44 to 31.97)			
Smoking/nicotine status - Missing|	10.0 (0 to 99999)			
Substance user-Current|	11.1 (0.28 to 48.25)			
Substance user-Former|	15.3 (7.22 to 26.99)			
Substance user-Never|	18.6 (8.39 to 33.40)			
HPV status-Positive|	29.4 (15.10 to 47.48)			
HPV status-Negative|	10.9 (4.51 to 21.25)			
HPV status-Missing|	7.7 (0 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Best objective response

End point title	Best objective response

End point description:

Best objective response based on BICR assessments according to RECIST v1.1. Response required confirmation after 4 weeks. Unconfirmed complete (CR) or partial response (PR) refers to CR or PR achieved but either no confirmation assessment was performed or a confirmation assessment was performed but response was not confirmed.

End point type	Secondary

End point timeframe:

12 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: % of participants				
number (not applicable)				
Response-Total|	16.2			
Response-Partial response (PR)|	15.3			
Response-Complete response (CR)|	0.9			
Non-response (NR)-Total|	83.8			
NR-Stable disease (SD)≥8 weeks-Total|	9.0			
NR-SD≥8 weeks-Unconfirmed CR or PR|	2.7			
NR-Stable disease (SD) ≥8 weeks-SD|	6.3			
NR-Progression-Total|	52.3			
NR-Progression-RECIST 1.1 progression|	25.2			
NR-Progression-Death|	27.0			
NR-Not evaluable-Total|	22.5			
NR-Not evaluable-SD<8 weeks|	19.8			
NR-Not evaluable-Incomplete post-baseline tests|	2.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response- Participants remaining in response

End point title	Duration of response- Participants remaining in response

End point description:

Participants remaining in response - based on BICR assessments according to RECIST v1.1. An ongoing response was defined as a patient who had documented objective response and was still alive and progression-free at the time of the data cut-off.

End point type	Secondary

End point timeframe:

12 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: % of participants				
number (not applicable)				
Remaining in response-3 months|	100			
Remaining in response-6 months|	76.5			
Remaining in response-9 months|	61.8			
Remaining in response-12 months|	37.1			
Ongoing response|	55.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of objective response in patients with objective response based on BICR assessments according to RECIST v1.1. Duration of response was the time from the first documentation of complete or partial response until the date of progression (which was subsequently confirmed), death, or the last evaluable RECIST assessment for patients that did not progress. An ongoing response was defined as a patient who had documented objective response and was still alive and progression-free at the time of the data cut-off.

End point type	Secondary

End point timeframe:

12 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
No. progressed or died within 12 months|	6			
No. progressed or died after 12 months|	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of response from first dose

End point title	Time to onset of response from first dose

End point description:

Time to onset of response in patients with objective response based on BICR assessments according to RECIST 1.1

End point type	Secondary

End point timeframe:

12 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
median (full range (min-max))	2.00 (1.64 to 9.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control at 6 months

End point title	Disease control at 6 months

End point description:

Disease control (DCR) at 6 months based on BICR assessments according to RECIST v1.1. DCR at 6 months was evaluated using 2 different approaches to the length of stable disease (SD): - Method 1: Patients who had a best objective response of complete response (CR) or partial response (PR) within 24 weeks or had demonstrated SD for a minimum interval of 24 weeks following the start of study treatment. - Method 2: Patients who had a best objective response of CR or PR within 24 weeks or had demonstrated SD for a minimum interval of 16 weeks following the start of study treatment.

End point type	Secondary

End point timeframe:

6 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: % of participants				
number (not applicable)				
METHOD 1 (M1): Disease control at 6 months|	23.4			
M1: No disease control at 6 months|	76.6			
M1: No disease control: Not evaluable/missing|	27.0			
METHOD 2 (M2): Disease control at 6 months|	33.3			
M2: No disease control at 6 months|	66.7			
M2: No disease control: Not evaluable/missing|	27.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression status based on BICR assessments according to RECIST v1.1 at time of PFS analysis. Progression was defined as the time from the date of first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdrew from therapy or received another anti-cancer therapy prior to progression.

End point type	Secondary

End point timeframe:

12 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: % of participants				
number (not applicable)				
No progression|	17.0			
No progression + under follow-up|	12.5			
Progression-Total|	83.0			
RECIST 1.1 progression|	50.0			
Death in absence of RECIST 1.1 progression|	33.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Survival status at time of overall survival analysis. 'Still in survival follow-up' includes patients known to be alive at data cut-off. 'Terminated prior to death' includes patients with unknown survival status, or who were lost to follow-up.

End point type	Secondary

End point timeframe:

12 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: % of participants				
number (not applicable)				
Still in survival follow-up|	24.1			
Terminated prior to death|	6.3			
Voluntary discontinuation by subject|	6.3			
Death|	69.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life

End point description:

Improvement in quality of life was assessed using European Organisation for Research and Treatment of Cancer (EORTC) questionnaires: -The impact of treatment on Health-Related Quality of Life, functioning, and symptoms was evaluated using the EORTC QLQ-C30 v3. -Head and neck cancer-specific symptoms were evaluated using the EORTC QLQ-H&N35. Function or global health status/quality of life improvement was defined as patients with 2 consecutive assessments at least 14 days apart that showed a clinically meaningful improvement (an increase from baseline score ≥10). Symptom improvement was defined as 2 consecutive assessments at least 14 days apart that showed a clinically meaningful improvement (a decrease from baseline score ≥10). Scale improvement was defined as patients with 2 consecutive assessments at least 14 days apart that showed a clinically meaningful improvement (a decrease from baseline score ≥10).

End point type	Secondary

End point timeframe:

12 months

End point values	MEDI4736			
Subject group type	Reporting group			
Number of subjects analysed	112			
Units: % of participants				
number (confidence interval 95%)				
EORTC QLQ-C30 Function-Physical|	17.1 (10.1 to 27.6)			
EORTC QLQ-C30 Function-Role|	22.9 (14.6 to 34.0)			
EORTC QLQ-C30 Function-Cognitive|	21.0 (12.7 to 32.6)			
EORTC QLQ-C30 Function-Emotional|	15.9 (9.1 to 26.3)			
EORTC QLQ-C30 Function-Social|	34.7 (24.9 to 45.9)			
EORTC QLQ-C30 Symptom-Fatigue|	21.3 (14.1 to 31.0)			
EORTC QLQ-C30 Symptom-Pain|	26.8 (18.4 to 37.3)			
EORTC QLQ-C30 Symptom-Nausea/vomiting|	32.3 (18.6 to 49.9)			
EORTC QLQ-C30 Global health status/QoL|	13.5 (8.1 to 21.8)			
EORTC QLQ-H&N35 Scale-Pain in the mouth|	24.6 (16.0 to 36.0)			
EORTC QLQ-H&N35 Scale-Swallowing|	19.4 (11.4 to 30.9)			
EORTC QLQ-H&N35 Scale-Senses|	34.3 (24.1 to 46.3)			
EORTC QLQ-H&N35 Scale-Speech|	28.4 (19.7 to 39.0)			
EORTC QLQ-H&N35 Scale-Social eating|	22.4 (14.1 to 33.7)			
EORTC QLQ-H&N35 Scale-Social contact|	17.2 (9.6 to 28.9)			
EORTC QLQ-H&N35 Scale-Sexuality|	25.7 (17.1 to 36.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the informed consent was signed through 90 days after the last dose of the last study treatment or until another therapy was initiated.

Adverse event reporting additional description:

AEs were reported spontaneously or in response to open questions, revealed by observation, or were changes from baseline/deterioration in tests and vital signs that met SAE criteria or led to IP discontinuation. AEs/SAEs were followed up for resolution after discontinuation or study completion and for as long as medically indicated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	MEDI4736 10 mg/kg

Reporting group description:

MEDI4736 monotherapy: Durvalumab was provided at a dose of 10 mg/kg using an intravenous solution every 2 weeks until 12 months, disease progression, toxicity, or patient decision to stop therapy

Serious adverse events	MEDI4736 10 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 112 (38.39%)		
number of deaths (all causes)	78		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	3 / 112 (2.68%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Localised oedema			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchopneumopathy			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Epistaxis			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung cyst			

subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Respiratory distress				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Stridor				

subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tachypnoea				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrostomy failure			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 112 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			

Cerebral infarction			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nerve compression			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular encephalopathy			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Constipation				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth haemorrhage				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal haemorrhage				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumatosis intestinalis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal infection				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 112 (3.57%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Pulmonary sepsis				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Wound infection				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 112 (0.89%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	2 / 112 (1.79%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	1 / 112 (0.89%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	MEDI4736 10 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 112 (83.04%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	7		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 112 (15.18%)		
occurrences (all)	18		
Fatigue			
subjects affected / exposed	26 / 112 (23.21%)		
occurrences (all)	27		
Localised oedema			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	6		
Mucosal inflammation			
subjects affected / exposed	6 / 112 (5.36%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 112 (10.71%)		
occurrences (all)	13		
Dyspnoea			

subjects affected / exposed	15 / 112 (13.39%)		
occurrences (all)	18		
Oropharyngeal pain			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	7		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	12		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 112 (6.25%)		
occurrences (all)	7		
Weight decreased			
subjects affected / exposed	13 / 112 (11.61%)		
occurrences (all)	13		
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 112 (9.82%)		
occurrences (all)	13		
Headache			
subjects affected / exposed	10 / 112 (8.93%)		
occurrences (all)	14		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 112 (16.07%)		
occurrences (all)	19		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	22 / 112 (19.64%)		
occurrences (all)	27		
Diarrhoea			
subjects affected / exposed	16 / 112 (14.29%)		
occurrences (all)	28		
Dysphagia			

subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	11 / 112 (9.82%) 11 22 / 112 (19.64%) 28 13 / 112 (11.61%) 19		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 8 / 112 (7.14%) 8 12 / 112 (10.71%) 14 7 / 112 (6.25%) 7		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 15 / 112 (13.39%) 15		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	 10 / 112 (8.93%) 15 7 / 112 (6.25%) 7 6 / 112 (5.36%) 6		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 7 / 112 (6.25%) 10		

Urinary tract infection subjects affected / exposed occurrences (all)	10 / 112 (8.93%) 10		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	18 / 112 (16.07%) 21		
Hypercalcaemia subjects affected / exposed occurrences (all)	10 / 112 (8.93%) 10		
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 112 (6.25%) 9		
Hypomagnesaemia subjects affected / exposed occurrences (all)	10 / 112 (8.93%) 15		
Hyponatraemia subjects affected / exposed occurrences (all)	8 / 112 (7.14%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2014	Updated study drug discontinuation requirements and sample collection schedule. Clarification of disease progression definition and PRO assessment. Inclusion of guidelines surrounding management of patients with hypersensitivity. Amended assessment language to be in alignment with other durvalumab studies.
24 November 2014	Updated inclusion and exclusion criteria surrounding previous treatment and laboratory testing. Clarification of required physical examination and vital sign assessments.
12 February 2015	Updated definition of full analysis set population and details surrounding interim analysis. Clarification of triiodothyronine and thyroxine testing requirements, consent process for PD-L1 testing and vital signs collection schedule.
27 February 2015	Updated sample size calculation, statistical analysis descriptions and vital signs assessment schedule. Clarification of PK sampling follow-up, AE follow-up schedule and inclusion and exclusion criteria. Removal of secondary endpoint relating to deep sustained response as this was not required to demonstrate durability of response. Specification of assay used to determine PD-L1 status.
06 August 2015	Updated requirements for PD-L1 sampling, required number of screened patients, survival status and PRO follow-up schedules, toxicity management guidelines, prohibited medication list and information surrounding durvalumab identity and preparation. Clarification of inclusion and exclusion criteria.
12 February 2016	Updated patient population and target population text. Estimated date of last patient last visit, scan submission and study drug discontinuation details were updated. Clarification of PD confirmation schedule, data cut-off and statistical methods for primary efficacy analysis text. The method of analysis for study endpoints was changed from immune-related response criteria to immune-related Response Evaluation Criteria in Solid Tumors version 1.1. Quality-of-life assessments were moved from secondary to exploratory objectives.
20 September 2017	Updated estimated date of last patient last visit. Addition of overall survival extension period and end of analysis sub-sections to detail the objectives of the OS extension period and the final analysis.
18 December 2017	Updated text was added to align with the updated investigator brochure. The dosing modification and toxicity management guidelines were updated to the most recent version. Text was updated to allow sites greater flexibility in the timing of survival calls post-data cut-off. Clarification of SAE variable collection and updated text to reflect the most recent immune-related AE terminology. Addition of section relating to follow-up status for withdrawn consent and lost to follow-up patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported