Clinical trial results:
A Phase II, Non-comparative, Open label, Multi-centre, International Study of MEDI4736, in Patients with Locally Advanced or Metastatic Non Small Cell Lung Cancer (Stage IIIB IV) Who Have Received at Least Two Prior Systemic Treatment Regimens Including One Platinum based Chemotherapy Regimen (ATLANTIC)

Summary

EudraCT number	2013-005427-16
Trial protocol	IT CZ DE GB HU BE AT ES PL
Global end of trial date	26 March 2025

Results information

Result version number	v1 (current)
This version publication date	24 October 2025
First version publication date	24 October 2025

Trial information

Trial identification

Sponsor protocol code	D4191C00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02087423
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, MD 20878
Public contact	Phillip Dennis, MD, PhD, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Phillip Dennis, MD, PhD, AstraZeneca, ClinicalTrialTransparency@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	07 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2016
Global end of trial reached?	Yes
Global end of trial date	26 March 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of durvalumab (MEDI4736) treatment in terms of Objective Response Rate (ORR) in programmed cell death ligand-1 (PD-L1) positive patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).

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/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 February 2014
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	Italy: 70
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Belgium: 34
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Korea, Republic of: 55
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Singapore: 13
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Philippines: 4
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Canada: 16
Worldwide total number of subjects	444
EEA total number of subjects	229

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)	265
From 65 to 84 years	178
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First patient in: 25 Feb 2014; Last patient in: 28 Dec 2015. Primary Analysis data cut-off (DCO): 03 Jun 2016; Final Analysis DCO: 7 Nov 2017. Patients were treated with durvalumab (10 milligrams [mg] / kilogram [kg] every 2 weeks [Q2W] intravenously [iv]). 101 sites in 16 countries treated patients in this study.

Pre-assignment

Screening details:

Patients were enrolled in 3 cohorts. Cohort enrolment was dependent upon epidermal growth factor receptor (EGFR) / anaplastic lymphoma kinase (ALK) status and PD-L1 expression level (percent of tumor cells [TC] with membrane staining).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (EGFR/ALK+)

Arm description:

Consisted of patients who were EGFR/ALK positive and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.

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

Dosage and administration details:

Patients received durvalumab 10 mg/kg Q2W iv.

Arm title	Cohort 2

Arm description:

Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.

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

Dosage and administration details:

Patients received durvalumab 10 mg/kg Q2W iv.

Arm title	Cohort 3 (TC >= 90%)

Arm description:

Consisted of patients who were EGFR/ALK wild type/unknown and prospectively determined to be PD-L1 high (TC >=90%).

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

Dosage and administration details:

Patients received durvalumab 10 mg/kg Q2W iv.

Number of subjects in period 1	Cohort 1 (EGFR/ALK+)	Cohort 2	Cohort 3 (TC >= 90%)
Started	111	265	68
Completed 12 months of treatment	18	60	26
Completed	0	0	0
Not completed	111	265	68
Terminated from study at final DCO	23	36	25
Consent withdrawn by subject	20	20	3
Death	68	207	40
Lost to follow-up	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (EGFR/ALK+)
Reporting group description:	
Consisted of patients who were EGFR/ALK positive and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.	
Reporting group title	Cohort 2
Reporting group description:	
Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.	
Reporting group title	Cohort 3 (TC >= 90%)
Reporting group description:	
Consisted of patients who were EGFR/ALK wild type/unknown and prospectively determined to be PD-L1 high (TC >=90%).	

Reporting group values	Cohort 1 (EGFR/ALK+)	Cohort 2	Cohort 3 (TC >= 90%)
Number of subjects	111	265	68
Age Categorical			
age groups of <=18, between 18 and 65, >=65,			
Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	66	155	44
>=65 years	45	110	24
Age Continuous			
Units: years			
median	61.0	62.0	61.0
standard deviation	± 11.45	± 9.35	± 10.58
Sex: Female, Male			
Units: Subjects			
Female	70	103	29
Male	41	162	39
Race/Ethnicity, Customized			
Units: Subjects			
White	44	212	42
Black or African American	1	2	2
Asian	66	51	24
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	6	19	2
Not Hispanic or Latino	105	246	66
Weight group			
Units: Subjects			
<70 kg	81	146	40
Between 70 and 90 kg	27	97	21
>90 kg	3	22	7
WHO performance status			

Units: Subjects			
(0) Normal activity	45	86	19
(1) Restricted activity	65	178	49
(2) In bed <=50% of the time	1	1	0
(3) In bed >50% of the time	0	0	0
(4) 100% bed ridden	0	0	0
Histology type Units: Subjects			
Squamous	1	55	20
Non-squamous	110	210	48
AJCC staging at initial diagnosis			
Per tumor, node, metastasis (TNM) staging system as specified by American Joint Committee on Cancer (AJCC). The staging is determined by a number of different parameters and the higher the staging the worse the prognosis for survival.			
Units: Subjects			
Stage IA	2	3	0
Stage IB	0	4	0
Stage II	0	1	0
Stage IIA	1	1	1
Stage IIB	0	5	0
Stage III	0	1	0
Stage IIIA	9	13	5
Stage IIIB	8	28	9
Stage IV	90	208	53
Missing	1	1	0
Best response to previous therapy			
based on the last therapy received prior to entering the study			
Units: Subjects			
complete response	0	1	0
partial response	31	39	18
stable disease	34	86	18
progression	38	114	26
non-evaluable	2	15	2
not applicable	6	10	4
Time from informed consent to first dose Units: Subjects			
<=14 days	21	68	7
Between 14 and 21 days	24	73	13
between 21 and 42 days	65	111	45
> 42 days	1	13	3
Overall disease classification			
either patient has any metastatic site of disease or has only locally advanced sites of disease			
Units: Subjects			
Metastatic	102	245	61
Locally advanced	9	20	7
PD-L1 expression level			
% of tumor cells with membrane staining for PD-L1			
Units: Subjects			
Positive (>=25%)|	77	149	68
Negative (<25%)|	30	95	0
Unknown|	3	21	0

Missing|	1	0	0
Smoking history			
Patients who checked options Cigarettes, Cigarillos, Cigars, Pipe Tobacco, or Tobacco for Smoking are considered smokers.			
Units: Subjects			
Non-smoker	65	39	9
Smoker	46	225	59
Missing	0	1	0
Number of regimens of previous anti-cancer therapy			
Units: Number of regimens			
median	3	3	2
standard deviation	± 2.00	± 1.38	± 0.80
Weight			
Units: kg			
median	59	68	66
standard deviation	± 14.15	± 14.52	± 15.79

Reporting group values	Total		
Number of subjects	444		
Age Categorical			
age groups of <=18, between 18 and 65, >=65,			
Units: Subjects			
<=18 years	0		
Between 18 and 65 years	265		
>=65 years	179		
Age Continuous			
Units: years			
median			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	202		
Male	242		
Race/Ethnicity, Customized			
Units: Subjects			
White	298		
Black or African American	5		
Asian	141		
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	27		
Not Hispanic or Latino	417		
Weight group			
Units: Subjects			
<70 kg	267		
Between 70 and 90 kg	145		
>90 kg	32		
WHO performance status			
Units: Subjects			
(0) Normal activity	150		
(1) Restricted activity	292		

(2) In bed <=50% of the time	2		
(3) In bed >50% of the time	0		
(4) 100% bed ridden	0		
Histology type Units: Subjects			
Squamous	76		
Non-squamous	368		
AJCC staging at initial diagnosis			
Per tumor, node, metastasis (TNM) staging system as specified by American Joint Committee on Cancer (AJCC). The staging is determined by a number of different parameters and the higher the staging the worse the prognosis for survival.			
Units: Subjects			
Stage IA	5		
Stage IB	4		
Stage II	1		
Stage IIA	3		
Stage IIB	5		
Stage III	1		
Stage IIIA	27		
Stage IIIB	45		
Stage IV	351		
Missing	2		
Best response to previous therapy			
based on the last therapy received prior to entering the study			
Units: Subjects			
complete response	1		
partial response	88		
stable disease	138		
progression	178		
non-evaluable	19		
not applicable	20		
Time from informed consent to first dose Units: Subjects			
<=14 days	96		
Between 14 and 21 days	110		
between 21 and 42 days	221		
> 42 days	17		
Overall disease classification			
either patient has any metastatic site of disease or has only locally advanced sites of disease			
Units: Subjects			
Metastatic	408		
Locally advanced	36		
PD-L1 expression level			
% of tumor cells with membrane staining for PD-L1			
Units: Subjects			
Positive (>=25%)|	294		
Negative (<25%)|	125		
Unknown|	24		
Missing|	1		
Smoking history			
Patients who checked options Cigarettes, Cigarillos, Cigars, Pipe Tobacco, or Tobacco for Smoking are			

considered smokers.			
Units: Subjects			
Non-smoker	113		
Smoker	330		
Missing	1		
Number of regimens of previous anti-cancer therapy Units: Number of regimens median standard deviation	- -		
Weight Units: kg median standard deviation	- -		

End points

End points reporting groups

Reporting group title	Cohort 1 (EGFR/ALK+)

Reporting group description:

Consisted of patients who were EGFR/ALK positive and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.

Reporting group title	Cohort 2

Reporting group description:

Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.

Reporting group title	Cohort 3 (TC >= 90%)

Reporting group description:

Consisted of patients who were EGFR/ALK wild type/unknown and prospectively determined to be PD-L1 high (TC >=90%).

Subject analysis set title	Cohort 1 (EGFR/ALK+) PD-L1+ (>=25%) (FAS - evaluable per ICR)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK mutation positive and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). Patients with PD-L1 TC>=90% are included in this group.

Analysis population: "Full analysis set (FAS) - evaluable for response per Independent Central Review (ICR)" set, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the ICR.

Subject analysis set title	Cohort 1 (EGFR/ALK+) PD-L1- (<25%) (FAS - evaluable per ICR)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK mutation positive and retrospectively or prospectively determined to be PD-L1 low/neg (TC <25%).

Analysis population: "FAS – evaluable for response per ICR" set, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the ICR.

Subject analysis set title	Cohort 2 PD-L1+ (>=25%) (FAS - evaluable per ICR)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). Patients with PD-L1 TC>=90% are included in this group.

Analysis population: "FAS – evaluable for response per ICR" set, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the ICR.

Subject analysis set title	Cohort 2 PD-L1- (<25%) (FAS - evaluable per ICR)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 low/neg (TC <25%).

Analysis population: "FAS – evaluable for response per ICR" set, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the ICR.

Subject analysis set title	Cohort 3 (TC>=90%) (FAS - evaluable per ICR)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK wild type/unknown and prospectively determined to be PD-L1 high (TC>=90%).

Analysis population: "FAS – evaluable for response per ICR" set, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the ICR.

Subject analysis set title	Cohort 1 (EGFR/ALK+) PD-L1+ (>=25%) (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK mutation positive and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). Patients with PD-L1 TC>=90% are included in this group.

Analysis population: FAS, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the Investigator site assessment.

Subject analysis set title	Cohort 1 (EGFR/ALK+) PD-L1- (<25%) (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK mutation positive and retrospectively or prospectively determined to be PD-L1 low/neg (TC <25%).

Analysis population: FAS, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the Investigator site assessment.

Subject analysis set title	Cohort 2 PD-L1+ (>=25%) (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). Patients with PD-L1 TC>=90% are included in this group.

Analysis population: FAS, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the Investigator site assessment.

Subject analysis set title	Cohort 2 PD-L1- (<25%) (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 low/neg (TC <25%).

Analysis population: FAS, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the Investigator site assessment.

Subject analysis set title	Cohort 3 (TC>=90%) (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Consisted of patients who were EGFR/ALK wild type/unknown and prospectively determined to be PD-L1 high (TC>=90%).

Analysis population: FAS, which included all treated patients who had a baseline tumor assessment and had measurable disease at baseline according to the Investigator site assessment.

Primary: Objective Response Rate (ORR)

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

End point description:

Patients commenced treatment with durvalumab on Day 1 and continued on a Q2W schedule for a maximum of 12 months. Tumor assessments using computed tomography / magnetic resonance imaging were performed every 8 weeks. Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) measurements as given by the Independent Central Review (ICR) were used to derive the primary variable of ORR.

End point type	Primary

End point timeframe:

Responses recorded during initial 12 month treatment period (up to primary analysis DCO)

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: Only descriptive analysis was planned and performed for analysis of the primary end point

End point values	Cohort 1 (EGFR/ALK+) PD-L1+ (>=25%) (FAS - evaluable per ICR)	Cohort 1 (EGFR/ALK+) PD-L1- (<25%) (FAS - evaluable per ICR)	Cohort 2 PD-L1+ (>=25%) (FAS - evaluable per ICR)	Cohort 2 PD-L1- (<25%) (FAS - evaluable per ICR)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	74	28	146	93
Units: % of patients evaluable for response				
number (confidence interval 95%)	12.2 (5.7 to 21.8)	3.6 (0.1 to 18.3)	16.4 (10.8 to 23.5)	7.5 (3.1 to 14.9)

End point values	Cohort 3 (TC>=90%) (FAS - evaluable per ICR)			
Subject group type	Subject analysis set			
Number of subjects analysed	68			
Units: % of patients evaluable for response				
number (confidence interval 95%)	30.9 (20.2 to 43.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR (per RECIST 1.1 as assessed by the ICR) is defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed). TTR was analyzed in patients with objective response in Cohort 2 only.

End point type	Secondary

End point timeframe:

Responses recorded during initial 12 month treatment period (up to primary analysis DCO)

End point values	Cohort 2 PD-L1+ (>=25%) (FAS - evaluable per ICR)	Cohort 2 PD-L1- (<25%) (FAS - evaluable per ICR)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	7		
Units: Months				
median (full range (min-max))	1.9 (1.6 to 16.7)	2.1 (1.7 to 13.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time from the date of first dose until death due to any cause (ie, date of death or censoring – date of first dose + 1). Results are reported as median OS, calculated using the Kaplan-Meier methodology. "99999" in the data table indicates that the upper limit confidence interval was not reached.

End point type	Secondary

End point timeframe:

From date of first treatment until final DCO (up to approximately 3 years 8 months)

End point values	Cohort 1 (EGFR/ALK+) PD-L1+ (>=25%) (FAS)	Cohort 1 (EGFR/ALK+) PD-L1- (<25%) (FAS)	Cohort 2 PD-L1+ (>=25%) (FAS)	Cohort 2 PD-L1- (<25%) (FAS)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	77	30	149	94
Units: Months				
median (confidence interval 95%)	13.3 (6.3 to 24.5)	9.9 (4.2 to 13.3)	10.9 (8.6 to 13.6)	9.3 (5.9 to 10.8)

End point values	Cohort 3 (TC>=90%) (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Months				
median (confidence interval 95%)	13.2 (5.9 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

DoR (per RECIST 1.1 as assessed by the ICR) was defined as the time from the date of first documented response (which was subsequently confirmed) until the first date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). DoR was analyzed in patients with objective response in Cohort 2 only. "99999" in the data table indicates that either the median DoR value and/or the inter-quartile range value was not reached.

End point type	Secondary

End point timeframe:

Time from response to progression, death, or last assessment (up to approximately 2 years 3 months for the primary analysis DCO)

End point values	Cohort 2 PD-L1+ (>=25%) (FAS - evaluable per ICR)	Cohort 2 PD-L1- (<25%) (FAS - evaluable per ICR)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	7		
Units: Months				
median (inter-quartile range (Q1-Q3))	12.3 (7.5 to 99999)	99999 (7.2 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) observed up until 90 days following discontinuation of durvalumab or until the initiation of the first subsequent anticancer therapy following discontinuation of durvalumab (whichever occurred first).

Adverse event reporting additional description:

All-Cause Mortality is reported for the overall study period, up to the final DCO. Serious and Other (non-serious) TEAE data is reported for the initial treatment phase (maximum of 12 months of treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Cohort 1 (EGFR/ALK+)

Reporting group description:

Consisted of patients who were EGFR/ALK positive and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.

Reporting group title	Cohort 3 (TC >=90%)

Reporting group description:

Consisted of patients who were EGFR/ALK wild type/unknown and prospectively determined to be PD-L1 high (TC >=90%).

Reporting group title	Cohort 2

Reporting group description:

Consisted of patients who were EGFR/ALK wild type/unknown and retrospectively or prospectively determined to be PD-L1 high (TC >=25%). In addition, the cohort included patients enrolled prior to Amendment 1 who were retrospectively determined to be PD-L1 low/neg (TC <25%) or PD-L1 status unknown.

Serious adverse events	Cohort 1 (EGFR/ALK+)	Cohort 3 (TC >=90%)	Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 111 (16.22%)	24 / 68 (35.29%)	77 / 265 (29.06%)
number of deaths (all causes)	70	41	217
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			

subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	2 / 111 (1.80%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sudden death			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asthenia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	3 / 265 (1.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malaise			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 111 (0.00%)	2 / 68 (2.94%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 111 (0.90%)	2 / 68 (2.94%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Dyspnoea			
subjects affected / exposed	3 / 111 (2.70%)	0 / 68 (0.00%)	7 / 265 (2.64%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	4 / 265 (1.51%)
occurrences causally related to treatment / all	1 / 1	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 111 (0.90%)	1 / 68 (1.47%)	5 / 265 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 111 (0.90%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			

subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine output decreased			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 111 (0.90%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hip fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 111 (0.90%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Seizure			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 111 (0.00%)	2 / 68 (2.94%)	3 / 265 (1.13%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Dysphagia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			

subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	3 / 265 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nausea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal rupture			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice cholestatic			

subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic atrophy			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			

subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes insipidus			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	8 / 265 (3.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	3 / 265 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	2 / 265 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			

subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diverticulitis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal abscess			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 111 (0.90%)	0 / 68 (0.00%)	1 / 265 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	0 / 265 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1 (EGFR/ALK+)	Cohort 3 (TC >=90%)	Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 111 (86.49%)	60 / 68 (88.24%)	233 / 265 (87.92%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 111 (4.50%)	5 / 68 (7.35%)	11 / 265 (4.15%)
occurrences (all)	5	5	13
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 111 (2.70%)	5 / 68 (7.35%)	12 / 265 (4.53%)
occurrences (all)	3	5	14
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 111 (1.80%)	2 / 68 (2.94%)	14 / 265 (5.28%)
occurrences (all)	2	2	14
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 111 (3.60%)	0 / 68 (0.00%)	15 / 265 (5.66%)
occurrences (all)	4	0	15
Weight decreased			
subjects affected / exposed	3 / 111 (2.70%)	13 / 68 (19.12%)	22 / 265 (8.30%)
occurrences (all)	3	13	22
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 111 (5.41%)	4 / 68 (5.88%)	12 / 265 (4.53%)
occurrences (all)	6	6	18
Headache			
subjects affected / exposed	13 / 111 (11.71%)	6 / 68 (8.82%)	26 / 265 (9.81%)
occurrences (all)	15	6	32
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 111 (2.70%)	8 / 68 (11.76%)	43 / 265 (16.23%)
occurrences (all)	3	8	52
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 111 (12.61%)	4 / 68 (5.88%)	53 / 265 (20.00%)
occurrences (all)	15	4	76
Fatigue			

subjects affected / exposed	15 / 111 (13.51%)	20 / 68 (29.41%)	69 / 265 (26.04%)
occurrences (all)	16	31	80
Non-cardiac chest pain			
subjects affected / exposed	3 / 111 (2.70%)	4 / 68 (5.88%)	10 / 265 (3.77%)
occurrences (all)	4	5	15
Oedema peripheral			
subjects affected / exposed	7 / 111 (6.31%)	9 / 68 (13.24%)	25 / 265 (9.43%)
occurrences (all)	8	13	25
Pain			
subjects affected / exposed	1 / 111 (0.90%)	4 / 68 (5.88%)	8 / 265 (3.02%)
occurrences (all)	1	4	8
Pyrexia			
subjects affected / exposed	12 / 111 (10.81%)	12 / 68 (17.65%)	53 / 265 (20.00%)
occurrences (all)	14	16	81
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	7 / 111 (6.31%)	1 / 68 (1.47%)	12 / 265 (4.53%)
occurrences (all)	8	1	12
Constipation			
subjects affected / exposed	14 / 111 (12.61%)	16 / 68 (23.53%)	37 / 265 (13.96%)
occurrences (all)	15	19	45
Diarrhoea			
subjects affected / exposed	11 / 111 (9.91%)	9 / 68 (13.24%)	39 / 265 (14.72%)
occurrences (all)	14	10	53
Nausea			
subjects affected / exposed	14 / 111 (12.61%)	12 / 68 (17.65%)	46 / 265 (17.36%)
occurrences (all)	16	15	57
Vomiting			
subjects affected / exposed	13 / 111 (11.71%)	10 / 68 (14.71%)	27 / 265 (10.19%)
occurrences (all)	15	13	36
Abdominal pain			
subjects affected / exposed	5 / 111 (4.50%)	4 / 68 (5.88%)	10 / 265 (3.77%)
occurrences (all)	6	6	10
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	26 / 111 (23.42%)	13 / 68 (19.12%)	56 / 265 (21.13%)
occurrences (all)	32	16	67
Dysphonia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 68 (1.47%)	14 / 265 (5.28%)
occurrences (all)	0	1	15
Dyspnoea			
subjects affected / exposed	13 / 111 (11.71%)	7 / 68 (10.29%)	43 / 265 (16.23%)
occurrences (all)	14	10	46
Haemoptysis			
subjects affected / exposed	3 / 111 (2.70%)	4 / 68 (5.88%)	14 / 265 (5.28%)
occurrences (all)	3	6	20
Productive cough			
subjects affected / exposed	4 / 111 (3.60%)	4 / 68 (5.88%)	20 / 265 (7.55%)
occurrences (all)	4	4	23
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 111 (6.31%)	8 / 68 (11.76%)	19 / 265 (7.17%)
occurrences (all)	9	8	20
Pruritus			
subjects affected / exposed	9 / 111 (8.11%)	13 / 68 (19.12%)	27 / 265 (10.19%)
occurrences (all)	11	14	39
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 111 (1.80%)	2 / 68 (2.94%)	16 / 265 (6.04%)
occurrences (all)	2	2	16
Insomnia			
subjects affected / exposed	10 / 111 (9.01%)	5 / 68 (7.35%)	16 / 265 (6.04%)
occurrences (all)	12	5	19
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	11 / 111 (9.91%)	7 / 68 (10.29%)	17 / 265 (6.42%)
occurrences (all)	12	8	18
Hypothyroidism			
subjects affected / exposed	11 / 111 (9.91%)	8 / 68 (11.76%)	19 / 265 (7.17%)
occurrences (all)	14	9	24
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	7 / 111 (6.31%)	5 / 68 (7.35%)	21 / 265 (7.92%)
occurrences (all)	7	6	25
Back pain			
subjects affected / exposed	11 / 111 (9.91%)	8 / 68 (11.76%)	23 / 265 (8.68%)
occurrences (all)	11	10	24
Musculoskeletal pain			
subjects affected / exposed	4 / 111 (3.60%)	3 / 68 (4.41%)	16 / 265 (6.04%)
occurrences (all)	4	4	21
Neck pain			
subjects affected / exposed	3 / 111 (2.70%)	7 / 68 (10.29%)	8 / 265 (3.02%)
occurrences (all)	3	7	8
Pain in extremity			
subjects affected / exposed	5 / 111 (4.50%)	2 / 68 (2.94%)	18 / 265 (6.79%)
occurrences (all)	5	2	21
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 111 (1.80%)	4 / 68 (5.88%)	4 / 265 (1.51%)
occurrences (all)	2	5	4
Upper respiratory tract infection			
subjects affected / exposed	6 / 111 (5.41%)	6 / 68 (8.82%)	8 / 265 (3.02%)
occurrences (all)	9	6	8
Urinary tract infection			
subjects affected / exposed	4 / 111 (3.60%)	3 / 68 (4.41%)	15 / 265 (5.66%)
occurrences (all)	4	4	19
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 111 (4.50%)	11 / 68 (16.18%)	12 / 265 (4.53%)
occurrences (all)	6	18	13
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	15 / 111 (13.51%)	12 / 68 (17.65%)	71 / 265 (26.79%)
occurrences (all)	15	12	77
Hyponatraemia			
subjects affected / exposed	2 / 111 (1.80%)	4 / 68 (5.88%)	14 / 265 (5.28%)
occurrences (all)	2	5	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2014	• To increase the number of patients (and also the number of sites) expected to undergo a pre-screening assessment in order to recruit the required number of patients fulfilling the new selection criterion of a PD-L1 high tumor. • To remove patient reported outcomes as variables in the study.
28 November 2014	• Study design was changed to include a third cohort of patients with PD-L1 TC ≥90%. • Extension of recruitment period due to addition of a third patient cohort. The new Cohort 3 (TC ≥90%) was not to start enrolling patients until Cohort 2 was fully enrolled. • Addition of the exploratory analysis of ORR, OS, and Progression Free Survival in patients with PD-L1 low/neg tumors.
10 April 2015	• To define the primary objective by cohort. • To add key secondary objectives by cohort on the evaluation of the clinical benefit of durvalumab in non-squamous PD-L1 high patients and non-squamous PD-L1 unselected patients. To add other secondary objectives to include the PD-L1 low/neg patients, non-squamous PD-L1 low/neg patients, and PD-L1 unselected patients. To add a footnote to define when objective tumor response should be confirmed because ORR is now included in the secondary objectives section for certain patient populations. • To amend the exploratory objective describing the assessment of efficacy in PD-L1 low/neg patients in Cohort 1 (EGFR/ALK+). • To remove the endpoint of "deep sustained response." • To add time to response as an endpoint.
19 November 2015	• To add a secondary objective to assess efficacy in a combined population of Cohorts 2 and 3 who were PD-L1 (TC ≥90%) and to modify the subgroups in Cohort 2 for the secondary efficacy objectives. • To define specific eligibility criteria for patients who were treated through progression or who achieved disease control and restarted treatment upon evidence of progression of disease. • To update the description of the statistical analyses based on the changes to the objectives and to clarify the timing of the final analysis of OS. • To add amylase and lipase laboratory assessments and to revise the frequency of collections for circulating soluble factors and miRNA/mRNA (ie, microRNA/messenger RNA) assessments.
11 August 2017	• To clarify the timing of scans following the final OS DCO, to reflect the revised duration of re-treatment and to clarify re-treatment eligibility. • To clarify end-of-study procedures for patients who continue in follow-up or re-treatment following the final OS DCO. • To update toxicity management guidelines. • To clarify the conduct of scans and other assessments for patients continuing treatment or re starting durvalumab treatment following the final OS DCO, and to clarify the revised duration of re-treatment. • To clarify that Interactive Voice/Web Response Systems will not be available following final OS DCO. • To clarify IP accountability, safety monitoring and reporting, data collection and patient assessments following final OS DCO. • To clarify that patients in survival follow-up will be withdrawn at the time of final OS DCO. • To provide guidance for Investigators. • To clarify the circumstances under which the study will end.
10 January 2018	• To update toxicity management guidelines. • To amend section regarding adverse events of special interest to align with updated safety information as found in the current durvalumab Investigator's Brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported