Clinical trial results:
A Phase III Randomized, Open-Label, Multi-Center, Global Study of MEDI4736 Monotherapy and MEDI4736 in Combination with Tremelimumab Versus Standard of Care Therapy in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Summary

EudraCT number	2014-003863-40
Trial protocol	HU CZ BE DE ES FR PL RO HR IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	06 February 2021
First version publication date	06 February 2021

Trial information

Trial identification

Sponsor protocol code	D4193C00002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02369874
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Forskargatan 18, Sodertalje, Sweden,
Public contact	Nassim Morsli, AstraZeneca, +44 7384 520046, nassim.morsli@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	Interim

Date of interim/final analysis	10 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of durvalumab + tremelimumab combination therapy versus standard of care (SoC) and durvalumab monotherapy versus SoC in terms of overall survival.

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 Conference on Harmonisation/ Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 65
Country: Number of subjects enrolled	United States: 40
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	France: 93
Country: Number of subjects enrolled	Spain: 69
Country: Number of subjects enrolled	Italy: 56
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Belgium: 43
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Romania: 42
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Taiwan: 21
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	Chile: 1
Worldwide total number of subjects	736
EEA total number of subjects	372

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)	514
From 65 to 84 years	222
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 1086 participants who enrolled and screened, 77 participants failed screening but were subsequently re-enrolled and re-screened. Of these 77, 56 were randomized and 21 failed re-screening. Overall, 736 patients were randomized to receive treatment with durvalumab + tremelimumab combination therapy, durvalumab monotherapy, or SoC therapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Durvalumab + Tremelimumab

Arm description:

Participants received 20 mg/kg durvalumab and 1 mg/kg tremelimumab combination therapy via intravenous (IV) infusion every 4 weeks (q4w) for up to 16 weeks. 4 weeks after completion of combination therapy, participants received dosing with durvalumab 10 mg/kg monotherapy every 2 weeks (q2w) until disease progression (PD).

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

Dosage and administration details:

20 mg/kg administered via intravenous (IV) infusion every 4 weeks (q4w) for 4 doses then 10 mg/kg via IV infusion q2w beginning 4 weeks after the last combination dose.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg administered via intravenous (IV) infusion every 4 weeks (q4w) for 4 doses (4 doses total).

Arm title	Durvalumab

Arm description:

Participants received 10 mg/kg durvalumab via intravenous (IV) infusion every 2 weeks (q2w) until disease progression (PD).

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

Dosage and administration details:

10 mg/kg administered via intravenous (IV) infusion every 2 weeks (q2w).

Arm title	Standard of Care (SoC)

Arm description:

Participants received monotherapy with 1 of the following therapies at the investigator’s discretion until disease progression (PD): cetuximab, a taxane, methotrexate, or a fluoropyrimidine.

Arm type	Active comparator
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m^2 administered via intravenous (IV) infusion on Day 0, then 250 mg/m^2 via IV infusion weekly thereafter.

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

Dosage and administration details:

40 mg/m^2 administered via intravenous (IV) infusion weekly.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m^2 administered via intravenous (IV) infusion weekly.

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2400 mg/m^2 administered via intravenous (IV) infusion over 46 hours every 2 weeks.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

40 mg/m2 administered via intravenous (IV) infusion weekly per the institution’s SoC.

Investigational medicinal product name	Tegafur/Gimeracil/Oteracil
Investigational medicinal product code	TS-1
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

80 mg/m^2 administered orally once daily for 28 days followed by a 14-day rest.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

1000 mg/m^2 administered orally twice daily for 7 days followed by a 7-day rest.

Number of subjects in period 1	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)
Started	247	240	249
Received Treatment	246	237	240
Completed	203	183	188
Not completed	44	57	61
Miscellaneous	1	1	-
Participant Ongoing	34	45	32
Consent withdrawn by subject	7	9	27
Lost to follow-up	2	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Durvalumab + Tremelimumab
Reporting group description:	
Participants received 20 mg/kg durvalumab and 1 mg/kg tremelimumab combination therapy via intravenous (IV) infusion every 4 weeks (q4w) for up to 16 weeks. 4 weeks after completion of combination therapy, participants received dosing with durvalumab 10 mg/kg monotherapy every 2 weeks (q2w) until disease progression (PD).	
Reporting group title	Durvalumab
Reporting group description:	
Participants received 10 mg/kg durvalumab via intravenous (IV) infusion every 2 weeks (q2w) until disease progression (PD).	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
Participants received monotherapy with 1 of the following therapies at the investigator's discretion until disease progression (PD): cetuximab, a taxane, methotrexate, or a fluoropyrimidine.	

Reporting group values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)
Number of subjects	247	240	249
Age, Customized Units: Subjects			
< 65 Years	174	169	171
>= 65 - < 75 Years	63	56	64
>= 75 Years	10	15	14
Age Continuous Units: Years			
arithmetic mean	59.9	59.0	59.5
standard deviation	± 9.14	± 10.07	± 10.37
Sex: Female, Male Units: Subjects			
Female	38	38	42
Male	209	202	207
Race/Ethnicity, Customized Units: Subjects			
Asian	33	35	45
Black Or African American	1	0	3
Other	4	5	3
White	204	198	189
Unknown or Not Reported	5	2	9
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	16	15	13
Not Hispanic or Latino	226	223	229
Unknown or Not Reported	5	2	7

Reporting group values	Total		
Number of subjects	736		

Age, Customized Units: Subjects			
< 65 Years	514		
>= 65 - < 75 Years	183		
>= 75 Years	39		
Age Continuous Units: Years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: Subjects			
Female	118		
Male	618		
Race/Ethnicity, Customized Units: Subjects			
Asian	113		
Black Or African American	4		
Other	12		
White	591		
Unknown or Not Reported	16		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	44		
Not Hispanic or Latino	678		
Unknown or Not Reported	14		

End points

End points reporting groups

Reporting group title	Durvalumab + Tremelimumab
Reporting group description:	
Participants received 20 mg/kg durvalumab and 1 mg/kg tremelimumab combination therapy via intravenous (IV) infusion every 4 weeks (q4w) for up to 16 weeks. 4 weeks after completion of combination therapy, participants received dosing with durvalumab 10 mg/kg monotherapy every 2 weeks (q2w) until disease progression (PD).	
Reporting group title	Durvalumab
Reporting group description:	
Participants received 10 mg/kg durvalumab via intravenous (IV) infusion every 2 weeks (q2w) until disease progression (PD).	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
Participants received monotherapy with 1 of the following therapies at the investigator's discretion until disease progression (PD): cetuximab, a taxane, methotrexate, or a fluoropyrimidine.	

Primary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS is defined as the time from the date of randomization until death due to any cause. OS was analyzed for the full analysis set, regardless of programmed death-ligand 1 (PD-L1) status.	
End point type	Primary
End point timeframe:	
September 2015 to September 2018 (36 months)	

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	240	249	
Units: Months				
median (confidence interval 95%)	6.5 (5.5 to 8.2)	7.6 (6.1 to 9.8)	8.3 (7.3 to 9.2)	

Statistical analyses

Statistical analysis title	Combo therapy vs. SoC
Comparison groups	Durvalumab + Tremelimumab v Standard of Care (SoC)
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7624
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.26

Statistical analysis title	Mono therapy vs. SoC
Comparison groups	Durvalumab v Standard of Care (SoC)
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1993
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.08

Secondary: Overall survival (OS) in PD-L1 negative participants

End point title	Overall survival (OS) in PD-L1 negative participants

End point description:

OS is defined as the time from the date of randomization until death due to any cause. PD-L1 negative was defined as <25% of tumor cells with membrane staining for PD-L1 at any intensity.

End point type	Secondary

End point timeframe:

September 2015 to September 2018 (36 months)

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	172	177	
Units: Months				
median (confidence interval 95%)	7.8 (5.9 to 10.3)	7.6 (6.2 to 9.5)	8.0 (6.7 to 8.9)	

Statistical analyses

Statistical analysis title	Combo therapy vs. SoC
Comparison groups	Durvalumab + Tremelimumab v Standard of Care (SoC)

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.459
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.17

Statistical analysis title	Combo therapy vs. mono therapy
Comparison groups	Durvalumab + Tremelimumab v Durvalumab
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.36

Secondary: Overall survival (OS) in PD-L1 positive participants

End point title	Overall survival (OS) in PD-L1 positive participants

End point description:

OS is defined as the time from the date of randomization until death due to any cause. PD-L1 positive was defined as ≥25% of tumor cells with membrane staining for PD-L1 at any intensity.

End point type	Secondary

End point timeframe:

September 2015 to September 2018 (36 months)

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	68	72	
Units: Months				
median (confidence interval 95%)	4.8 (3.3 to 6.4)	9.8 (4.3 to 14.1)	9.0 (6.8 to 9.2)	

Statistical analyses

Statistical analysis title	Mono therapy vs. SoC
Comparison groups	Durvalumab v Standard of Care (SoC)
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.39

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

PFS was defined as the time from the date of randomization until the date of objective disease progression or death based on investigator assessments, according to response evaluation criteria in solid tumors 1.1 (RECIST1.1). Objective disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

September 2015 to September 2018 (36 months)

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	240	249	
Units: Months				
median (confidence interval 95%)	2.0 (1.9 to 2.3)	2.1 (1.9 to 3.0)	3.7 (3.1 to 3.7)	

Statistical analyses

Statistical analysis title	Combo therapy vs. SoC
Comparison groups	Durvalumab + Tremelimumab v Standard of Care (SoC)

Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.33

Statistical analysis title	Mono therapy vs. SoC
Comparison groups	Durvalumab v Standard of Care (SoC)
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.25

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

The percentage of participants who experienced an objective response (complete response [CR] or partial response [PR]), based on investigator assessments according to response evaluation criteria in solid tumors 1.1 (RECIST1.1). A CR was defined as the disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm. A PR was defined as at least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Assessed at randomisation and every 8 weeks thereafter

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	240	249	
Units: Percentage of participants				
number (confidence interval 95%)	18.2 (13.6 to 23.6)	17.9 (13.3 to 23.4)	17.3 (12.8 to 22.5)	

Statistical analyses

Statistical analysis title	Combo therapy vs. SoC
Comparison groups	Durvalumab + Tremelimumab v Standard of Care (SoC)
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.7

Statistical analysis title	Mono therapy vs. SoC
Comparison groups	Durvalumab v Standard of Care (SoC)
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.68

Secondary: Duration of response (DoR)	
End point title	Duration of response (DoR)
End point description:	
Median DoR, in months, based on investigator assessments, according to response evaluation criteria in solid tumors 1.1 (RECIST1.1). A complete response was defined as the disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm. A partial response was defined as at least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters. Values of 99999 represent N/A.	
End point type	Secondary
End point timeframe:	
September 2015 to September 2018 (36 months)	

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	43	43	
Units: Months				
median (inter-quartile range (Q1-Q3))	7.4 (2.8 to 99999)	12.9 (5.6 to 99999)	3.7 (1.9 to 5.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

6 Months: The percentage of participants who had a best objective response of complete response (CR) or partial response (PR) in the first 6 months or had demonstrated stable disease (SD) for a minimum interval of 24 weeks following randomization. 12 Months: The percentage of participants who had a best objective response of CR or PR within 12 months or had demonstrated SD for a minimum interval of 48 weeks following randomization. Objective response was based on investigator assessments, according to response evaluation criteria in solid tumors 1.1 (RECIST1.1). A CR was defined as the disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm. A PR was defined as at least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

Baseline up to 6 months; baseline up to 12 months

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	240	249	
Units: Percentage of participants				
number (not applicable)				
6 Months	25.1	24.2	24.9	
12 Months	20.6	18.8	18.9	

Statistical analyses

Statistical analysis title	Combo therapy vs. SoC

Statistical analysis description:

6 Month analysis

Comparison groups	Durvalumab + Tremelimumab v Standard of Care (SoC)

Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.52

Statistical analysis title	Mono therapy vs. SoC
Statistical analysis description: 6 Month analysis	
Comparison groups	Durvalumab v Standard of Care (SoC)
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.46

Statistical analysis title	Combo therapy vs. SoC
Statistical analysis description: 12 Month analysis	
Comparison groups	Durvalumab + Tremelimumab v Standard of Care (SoC)
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.75

Statistical analysis title	Mono therapy vs. SoC
Statistical analysis description: 12 Month analysis	

Comparison groups	Durvalumab v Standard of Care (SoC)
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.57

Secondary: Percentage of participants alive and progression free (APF)

End point title	Percentage of participants alive and progression free (APF)

End point description:

APF is defined as the percentage of participants who are alive and progression free at 6 months and 12 months after randomization. Estimates of progression free survival were based on investigator assessments according to response evaluation criteria in solid tumors 1.1 (RECIST1.1). Objective disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

Baseline up to 6 months; baseline up to 12 months

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	240	249	
Units: Percentage of participants				
number (confidence interval 95%)				
6 Months	22.5 (17.4 to 28.0)	25.1 (19.7 to 30.9)	23.3 (17.8 to 29.3)	
12 Months	11.0 (7.4 to 15.5)	14.4 (10.1 to 19.5)	5.7 (2.8 to 10.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants alive

End point title	Percentage of participants alive

End point description:

Percentage of participants alive at 12, 18 and 24 months using a Kaplan Meier estimate.

End point type	Secondary

End point timeframe:

12, 18 and 24 months

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	247	240	249	
Units: Percentage of participants				
number (confidence interval 95%)				
12 Months	30.4 (24.7 to 36.3)	37.0 (30.9 to 43.1)	30.5 (24.7 to 36.4)	
18 Months	21.0 (15.9 to 26.5)	25.4 (19.9 to 31.3)	17.8 (13.1 to 23.2)	
24 Months	13.3 (8.9 to 18.6)	18.4 (13.3 to 24.1)	10.3 (5.7 to 16.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) in PD-L1 negative participants

End point title	Progression free survival (PFS) in PD-L1 negative participants

End point description:

Number of participants with confirmed objective disease progression (PD) at the time of the participant's last evaluable response evaluation criteria in solid tumors 1.1 (RECIST1.1) assessment. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. PD-L1 negative was defined as <25% of tumor cells with membrane staining for PD-L1 at any intensity.

End point type	Secondary

End point timeframe:

September 2015 to September 2018 (36 months)

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	172	177	
Units: Participants	154	151	144	

Statistical analyses

Statistical analysis title	Combo therapy vs. mono therapy
Comparison groups	Durvalumab + Tremelimumab v Durvalumab
Number of subjects included in analysis	347

Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.21

Secondary: Objective response rate (ORR) in PD-L1 negative participants

End point title	Objective response rate (ORR) in PD-L1 negative participants

End point description:

The percentage of PD-L1 negative participants who experienced an objective response (complete response [CR] or partial response [PR]), based on investigator assessments according to response evaluation criteria in solid tumors 1.1 (RECIST1.1). A CR was defined as the disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm. A PR was defined as at least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters. PD-L1 negative was defined as <25% of tumor cells with membrane staining for PD-L1 at any intensity.

End point type	Secondary

End point timeframe:

Assessed at randomisation and every 8 weeks thereafter

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	175	172	177	
Units: Percentage of participants				
number (confidence interval 95%)	17.7 (12.4 to 24.2)	14.0 (9.1 to 20.0)	15.3 (10.3 to 21.4)	

Statistical analyses

Statistical analysis title	Combo therapy vs. mono therapy
Comparison groups	Durvalumab + Tremelimumab v Durvalumab
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	2.39

Secondary: Time to Deterioration in European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire, version 3 (EORTC QLQ-C30)

End point title	Time to Deterioration in European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire, version 3 (EORTC QLQ-C30)

End point description:

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce functional scales (e.g. physical), symptom scales (e.g. fatigue), and a global measure of health status. Each of the scales are measured from 0 to 100. Deterioration was defined as a 10-point decrease from baseline in a functioning or global health status/ quality of life score or a 10-point increase from baseline in a symptom score.

End point type	Secondary

End point timeframe:

September 2015 to September 2018 (36 months)

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	227	226	227	
Units: Months				
median (confidence interval 95%)				
Function - Physical	2.0 (1.9 to 3.2)	2.2 (1.9 to 3.5)	3.7 (2.3 to 4.6)	
Function - Role	1.9 (1.8 to 2.4)	2.0 (1.8 to 2.7)	3.7 (2.5 to 4.1)	
Function - Emotional	2.4 (1.9 to 3.7)	3.6 (2.5 to 4.9)	3.8 (3.2 to 4.9)	
Function - Cognitive	2.1 (1.8 to 2.8)	2.2 (1.9 to 3.4)	4.0 (3.2 to 5.5)	
Function - Social	2.1 (1.9 to 3.4)	2.0 (1.8 to 3.4)	3.7 (3.2 to 4.7)	
Symptom - Fatigue	1.8 (1.3 to 1.9)	1.4 (1.0 to 1.9)	1.9 (1.6 to 2.6)	
Symptom - Pain	1.9 (1.8 to 2.4)	2.5 (1.9 to 3.7)	3.7 (2.7 to 4.1)	
Symptom - Nausea/ Vomiting	2.6 (2.0 to 3.9)	3.9 (2.8 to 4.9)	4.0 (3.6 to 5.5)	
Global health status/QoL	1.9 (1.8 to 2.7)	2.8 (1.9 to 3.8)	3.5 (2.9 to 4.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration for European Organisation for Research and Treatment of Cancer 35-item head and neck quality of life questionnaire (EORTC QLQ-H&N35)

End point title	Time to Deterioration for European Organisation for Research and Treatment of Cancer 35-item head and neck quality of life questionnaire (EORTC QLQ-H&N35)

End point description:

The EORTC QLQ-H&N35 comprises of 35 questions to assess head and neck cancer symptoms (e.g. pain, swallowing). Deterioration was defined as a 10-point increase from baseline in the symptom score.

End point type	Secondary

End point timeframe:

September 2015 to September 2018 (36 months)

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	223	220	221	
Units: Months				
median (confidence interval 95%)				
Pain (Mouth/ Throat)	2.9 (2.4 to 3.8)	2.8 (2.6 to 3.7)	3.4 (2.7 to 4.0)	
Swallowing	2.6 (1.9 to 3.6)	2.8 (1.9 to 3.9)	3.7 (2.9 to 4.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants reporting one or more adverse events (AE)

End point title	Number of participants reporting one or more adverse events (AE)

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. Inclusive of AEs and serious AEs.

End point type	Secondary

End point timeframe:

First dose to last dose + 90 days or data cut off (up to 36 months)

End point values	Durvalumab + Tremelimumab	Durvalumab	Standard of Care (SoC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	246	237	240	
Units: Participants	232	214	229	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First dose to last dose + 90 days or data cut off (maximum exposure 32 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Durvalumab + Tremelimumab
Reporting group description:	
Participants received 20 mg/kg durvalumab and 1 mg/kg tremelimumab combination therapy via intravenous (IV) infusion every 4 weeks (q4w) for up to 16 weeks. 4 weeks after completion of combination therapy, participants received dosing with durvalumab 10 mg/kg monotherapy every 2 weeks (q2w) until disease progression (PD).	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
Participants received monotherapy with 1 of the following therapies at the investigator's discretion until disease progression (PD): cetuximab, a taxane, methotrexate, or a fluoropyrimidine.	
Reporting group title	Durvalumab
Reporting group description:	
Participants received 10 mg/kg durvalumab via intravenous (IV) infusion every 2 weeks (q2w) until disease progression (PD).	

Serious adverse events	Durvalumab + Tremelimumab	Standard of Care (SoC)	Durvalumab
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 246 (32.11%)	61 / 240 (25.42%)	69 / 237 (29.11%)
number of deaths (all causes)	206	199	186
number of deaths resulting from adverse events			
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	2 / 246 (0.81%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Embolism			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hypertension			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Superior vena cava syndrome			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	7 / 246 (2.85%)	2 / 240 (0.83%)	4 / 237 (1.69%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 4

deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Tumour necrosis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chest pain			
subjects affected / exposed	2 / 246 (0.81%)	0 / 240 (0.00%)	0 / 237 (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
Death			
subjects affected / exposed	2 / 246 (0.81%)	2 / 240 (0.83%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	1 / 2	0 / 2	1 / 2
deaths causally related to treatment / all	1 / 2	0 / 2	1 / 2
Facial pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Fatigue			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to	1 / 1	0 / 0	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	4 / 237 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Hyperthermia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Pain			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 246 (1.63%)	2 / 240 (0.83%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Confusional state			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hallucinations, mixed			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Injury, poisoning and procedural complications			
Abdominal wall wound			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Femur fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Fibula fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Gastrostomy tube site complication			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Nasal injury			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoradionecrosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Periprosthetic fracture			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Petroleum distillate poisoning			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Radius fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Stoma site haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tracheostomy malfunction			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
White blood cell count decreased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 246 (0.81%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Cardiac arrest			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Cardiac failure			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Left ventricular failure			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Respiratory, thoracic and mediastinal disorders			
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to	0 / 0	0 / 0	0 / 1

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Apnoea			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Asphyxia			
subjects affected / exposed	2 / 246 (0.81%)	3 / 240 (1.25%)	3 / 237 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 3
Bronchial haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	3 / 237 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	3 / 237 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Pleural effusion			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Pneumonia aspiration			
subjects affected / exposed	3 / 246 (1.22%)	2 / 240 (0.83%)	5 / 237 (2.11%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 6
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Pneumonitis			
subjects affected / exposed	3 / 246 (1.22%)	1 / 240 (0.42%)	3 / 237 (1.27%)
occurrences causally related to treatment / all	2 / 3	0 / 1	3 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	4 / 246 (1.63%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0

Respiratory distress			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	0 / 237 (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
Respiratory failure			
subjects affected / exposed	0 / 246 (0.00%)	3 / 240 (1.25%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Sleep apnoea syndrome			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 246 (2.03%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Haemorrhagic diathesis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 246 (0.00%)	2 / 240 (0.83%)	0 / 237 (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
Pancytopenia			

subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Thrombocytopenia			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery disease			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	3 / 246 (1.22%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Epilepsy			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (0.00%)

occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Horner's syndrome			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Loss of consciousness			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Seizure			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)

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 disorders			
Abdominal pain			
subjects affected / exposed	2 / 246 (0.81%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coeliac disease			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Colitis ischaemic			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Constipation			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Diarrhoea			
subjects affected / exposed	2 / 246 (0.81%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	4 / 246 (1.63%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric fistula			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Gastric ulcer perforation			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to	0 / 0	0 / 1	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Inguinal hernia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Mouth haemorrhage			
subjects affected / exposed	2 / 246 (0.81%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Tongue haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Vomiting			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Renal failure			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Urticaria			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Vasculitic ulcer			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Device occlusion			
subjects affected / exposed	0 / 246 (0.00%)	2 / 240 (0.83%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Trismus			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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			
Adrenal insufficiency			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Hypopituitarism			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 246 (0.41%)	2 / 240 (0.83%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 246 (0.81%)	2 / 240 (0.83%)	4 / 237 (1.69%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Hyponatraemia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
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			
Abscess neck			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Abscess oral			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Bacteraemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	3 / 246 (1.22%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to	1 / 1	0 / 0	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Gastroenteritis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 246 (0.41%)	1 / 240 (0.42%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 246 (0.00%)	2 / 240 (0.83%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Lung infection			
subjects affected / exposed	1 / 246 (0.41%)	2 / 240 (0.83%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Oesophageal infection			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Peritonitis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Pneumonia			
subjects affected / exposed	9 / 246 (3.66%)	9 / 240 (3.75%)	8 / 237 (3.38%)
occurrences causally related to treatment / all	0 / 9	0 / 9	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Postoperative wound infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	4 / 246 (1.63%)	1 / 240 (0.42%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 246 (1.22%)	4 / 240 (1.67%)	0 / 237 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Septic shock			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Staphylococcal infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 240 (0.42%)	0 / 237 (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
Stoma site infection			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 240 (0.00%)	0 / 237 (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
Subcutaneous abscess			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	2 / 237 (0.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 240 (0.00%)	1 / 237 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Durvalumab + Tremelimumab	Standard of Care (SoC)	Durvalumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	203 / 246 (82.52%)	207 / 240 (86.25%)	180 / 237 (75.95%)
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 246 (6.91%)	7 / 240 (2.92%)	11 / 237 (4.64%)
occurrences (all)	17	8	14

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 246 (6.10%)	17 / 240 (7.08%)	11 / 237 (4.64%)
occurrences (all)	20	28	11
Blood alkaline phosphatase increased			
subjects affected / exposed	14 / 246 (5.69%)	8 / 240 (3.33%)	7 / 237 (2.95%)
occurrences (all)	20	9	11
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 246 (6.10%)	14 / 240 (5.83%)	7 / 237 (2.95%)
occurrences (all)	17	23	8
Gamma-glutamyltransferase increased			
subjects affected / exposed	17 / 246 (6.91%)	12 / 240 (5.00%)	9 / 237 (3.80%)
occurrences (all)	18	19	11
Weight decreased			
subjects affected / exposed	27 / 246 (10.98%)	20 / 240 (8.33%)	31 / 237 (13.08%)
occurrences (all)	27	22	33
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 246 (10.57%)	19 / 240 (7.92%)	25 / 237 (10.55%)
occurrences (all)	27	22	26
Dyspnoea			
subjects affected / exposed	27 / 246 (10.98%)	19 / 240 (7.92%)	27 / 237 (11.39%)
occurrences (all)	27	21	29
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	55 / 246 (22.36%)	56 / 240 (23.33%)	47 / 237 (19.83%)
occurrences (all)	68	94	57
Leukopenia			
subjects affected / exposed	10 / 246 (4.07%)	13 / 240 (5.42%)	2 / 237 (0.84%)
occurrences (all)	19	42	3
Neutropenia			
subjects affected / exposed	11 / 246 (4.47%)	32 / 240 (13.33%)	4 / 237 (1.69%)
occurrences (all)	16	86	4
Thrombocytopenia			
subjects affected / exposed	11 / 246 (4.47%)	18 / 240 (7.50%)	5 / 237 (2.11%)
occurrences (all)	23	49	11

Nervous system disorders			
Headache			
subjects affected / exposed	11 / 246 (4.47%)	16 / 240 (6.67%)	13 / 237 (5.49%)
occurrences (all)	11	19	15
Neuropathy peripheral			
subjects affected / exposed	4 / 246 (1.63%)	24 / 240 (10.00%)	5 / 237 (2.11%)
occurrences (all)	4	26	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	51 / 246 (20.73%)	56 / 240 (23.33%)	42 / 237 (17.72%)
occurrences (all)	57	63	53
Fatigue			
subjects affected / exposed	40 / 246 (16.26%)	35 / 240 (14.58%)	31 / 237 (13.08%)
occurrences (all)	44	44	35
Mucosal inflammation			
subjects affected / exposed	2 / 246 (0.81%)	17 / 240 (7.08%)	3 / 237 (1.27%)
occurrences (all)	3	20	3
Pyrexia			
subjects affected / exposed	31 / 246 (12.60%)	29 / 240 (12.08%)	19 / 237 (8.02%)
occurrences (all)	35	42	23
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 246 (5.28%)	8 / 240 (3.33%)	7 / 237 (2.95%)
occurrences (all)	13	8	7
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	33 / 246 (13.41%)	29 / 240 (12.08%)	33 / 237 (13.92%)
occurrences (all)	37	29	40
Diarrhoea			
subjects affected / exposed	38 / 246 (15.45%)	32 / 240 (13.33%)	24 / 237 (10.13%)
occurrences (all)	50	42	46
Dysphagia			
subjects affected / exposed	20 / 246 (8.13%)	18 / 240 (7.50%)	28 / 237 (11.81%)
occurrences (all)	22	18	30

Nausea			
subjects affected / exposed	30 / 246 (12.20%)	41 / 240 (17.08%)	27 / 237 (11.39%)
occurrences (all)	36	47	29
Vomiting			
subjects affected / exposed	15 / 246 (6.10%)	20 / 240 (8.33%)	18 / 237 (7.59%)
occurrences (all)	16	24	23
Stomatitis			
subjects affected / exposed	5 / 246 (2.03%)	27 / 240 (11.25%)	11 / 237 (4.64%)
occurrences (all)	7	34	12
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 246 (0.00%)	29 / 240 (12.08%)	0 / 237 (0.00%)
occurrences (all)	0	30	0
Dermatitis acneiform			
subjects affected / exposed	2 / 246 (0.81%)	17 / 240 (7.08%)	4 / 237 (1.69%)
occurrences (all)	2	18	4
Pruritus			
subjects affected / exposed	23 / 246 (9.35%)	9 / 240 (3.75%)	10 / 237 (4.22%)
occurrences (all)	28	10	13
Rash			
subjects affected / exposed	18 / 246 (7.32%)	36 / 240 (15.00%)	19 / 237 (8.02%)
occurrences (all)	20	38	22
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	20 / 246 (8.13%)	23 / 240 (9.58%)	15 / 237 (6.33%)
occurrences (all)	20	24	16
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	32 / 246 (13.01%)	5 / 240 (2.08%)	33 / 237 (13.92%)
occurrences (all)	33	5	44
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	51 / 246 (20.73%)	48 / 240 (20.00%)	30 / 237 (12.66%)
occurrences (all)	51	56	33
Hypercalcaemia			
subjects affected / exposed	21 / 246 (8.54%)	7 / 240 (2.92%)	10 / 237 (4.22%)
occurrences (all)	21	8	12

Hypomagnesaemia			
subjects affected / exposed	3 / 246 (1.22%)	20 / 240 (8.33%)	8 / 237 (3.38%)
occurrences (all)	3	25	10
Hyponatraemia			
subjects affected / exposed	16 / 246 (6.50%)	8 / 240 (3.33%)	11 / 237 (4.64%)
occurrences (all)	16	8	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2015	Updates to the following: - Management of non-immune-related toxicity using dose modifications. - Stratification factors changed to include PD-L1 status. - 'Deep sustained response' (DSR) endpoint removed. - Change to pre-specify stratified log-rank test as primary method of analysis for OS and PFS in all-comers population, while retaining the weighted HR approach as a supportive analysis. - PD-L1 status added as a pre-specified subgroup analysis.
03 April 2015	Updates to the following: - Change to doses of durvalumab and tremelimumab in the combination arm. - Clarification of procedures regarding discontinuation or retreatment in cases of confirmed PD. - Modifications to eligibility criteria. - Changes to endpoints and assessments.
01 June 2015	Updates to the following: - Eligibility criteria modified. - Clarification that no further enrolment into the durvalumab monotherapy arm applies to patients with PD-L1-negative tumors, should external data suggest lack of benefit of durvalumab monotherapy in the PD-L1 negative population.
18 February 2016	Updates to the following: - Co-primary endpoint of PFS removed, leaving only a primary endpoint of OS (accordingly, the multiple testing procedure was simplified). - Primary objective clarified as assessment of durvalumab + tremelimumab vs SoC in PD-L1-positive and -negative patients (ie, regardless of PD-L1 status). (throughout the document). - Previous primary comparison included monotherapy vs SoC in PD-L1-positive patients. - Clarification of key secondary objectives. - PFS, ORR, DoR, DCR, APF6, APF12 to be based on Investigator assessment rather than BICR. - PRO measures reduced and prioritised for formal analysis. - PRO for CTCAE reduced from collection of 30 PRO-CTCAE symptoms to 11. - Eligibility criteria modified. - Removal of text referring to possibility of halting enrolment of PD-L1- negative patients into the durvalumab monotherapy arm. - Definition of disease progression now to include clinical disease progression as well as confirmed objective disease progression. - Removal of the requirement to confirm response (amended to objective response). - Addition of one interim analysis for OS at 80% maturity, when 314 death events have occurred across the combination and SoC arms. - Update sample size estimate calculation and statistical assumptions. - Added analysis of patients with subsequent anticancer therapy. - HPV testing and analysis of OS by HPV status in patients with oropharyngeal cancer only. - Addition of subgroup analysis by race. - Management of study drug-related toxicities modified. - The timing and procedures for scheduled assessments and/or study design were modified and clarified.

07 September 2016	Updates to the following: - Change from single primary objective of durvalumab + tremelimumab vs SoC in terms of OS to co-primary objectives of durvalumab + tremelimumab vs SoC in terms of OS and durvalumab monotherapy vs SoC in terms of OS. - Treatment in all arms to continue until progression. - Retreatment sections updated to only allow retreatment for patients on the combination arm, provided that progression occurs during the monotherapy portion of dosing. - The hypothesis testing is expected to be performed after ~11 months of follow-up instead of 10 months, and after ~375 death events have occurred instead of 392. The number of events that triggers the interim analysis was reduced from 314 to 300. - The requirement for a min of 300 patients with PD-L1-positive disease was removed and enrolment was to be based on the natural prevalence of PD-L1-positive and -negative patients. - Updated to clarify that the specified PD-L1 expression cut-off level will be used for the purpose of stratification, however the cut-off level to be used for the subgroup analyses by PD-L1 status and for determining the PD-L1- negative subgroup in the MTP may be different and will be determined from emerging data outside of this trial. - Updated to include text to allow the study to stop for superiority based on interim OS analysis. - DoR will be analysed by descriptive statistical and Kaplan Meier plots. - Primary tumor status, prior radiation therapy, use of chewing tobacco, oral snuff, and sublingual nicotine, smoking history, ECOG PS, prior lines of systemic therapy for treatment of HNSCC, and extent of disease added as subgroups for analysis. - Weighted estimate of the overall HR removed. - The sensitivity analyses and information on the ascertainment bias, subgroup analysis and its display on forest plot, and adjustment of significance level of testing were removed.
23 January 2018	Updates to the following: - Updates to various sections to align with the most current safety information per the update to the Investigator’s Brochure. - New section added for survival status for withdrawn consent and lost to follow-up patients. - Clarification to collection of variables for SAEs. - New section added to describe treatment with durvalumab after the final data cut-off. - Updates to allow sites more flexibility in timing of survival calls after data cut-off.
10 September 2018	Updates to the following (12-Dec-2018): - New section added to the CSP (Safety data to be collected following the final data cut-off of the study) to describe how safety data would be recorded for patients continuing to receive study drug after final data cut-off and database closure. - Treatment regimens text amended to clarify that patients currently receiving treatment with durvalumab may be transitioned to a roll-over or safety extension study after the analysis is finalized.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Multiple testing was performed for OS analysis in the intent-to-treat (ITT) population and OS analysis in the PD-L1 negative population for durvalumab + tremelimumab versus SoC only.

Notes: