



Clinical trial results:

A Phase III Randomized, Open-label, Multi-center, Global Study of MEDI4736 in Combination with Tremelimumab versus Standard of Care (EXTREME) in the Treatment of First-line Recurrent or Metastatic Squamous Cell Head and Neck Cancer Patients

Summary

EudraCT number	2015-003589-10
Trial protocol	SK GR DE GB ES BE PL AT FR PT BG IT
Global end of trial date	06 July 2020

Results information

Result version number	v1 (current)
This version publication date	05 February 2022
First version publication date	05 February 2022

Trial information

Trial identification

Sponsor protocol code	D419LC00001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02551159
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 July 2020

Is this the analysis of the primary completion data?	Yes
Primary completion date	06 July 2020
Global end of trial reached?	Yes
Global end of trial date	06 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of MEDI4736 monotherapy compared to Standard of Care (SoC) in terms of Overall Survival (OS)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 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	Russian Federation: 101
Country: Number of subjects enrolled	United States: 62
Country: Number of subjects enrolled	Ukraine: 61
Country: Number of subjects enrolled	France: 58
Country: Number of subjects enrolled	Korea, Republic of: 54
Country: Number of subjects enrolled	Japan: 52
Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	Taiwan: 48
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Canada: 38
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Greece: 26
Country: Number of subjects enrolled	India: 23
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	Viet Nam: 8
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Philippines: 2
Worldwide total number of subjects	823
EEA total number of subjects	301

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)	530
From 65 to 84 years	290
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Patients meeting all the eligibility criteria were randomized 2:1:1 to durvalumab plus tremelimumab combination therapy, durvalumab monotherapy or standard of care.

Pre-assignment

Screening details:

All screening/baseline procedures must be performed within 28 days before the first dose of treatment (Days -28 to -1)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Durvalumab + tremelimumab

Arm description:

tremelimumab (75 mg) via IV infusion every 4 weeks for a maximum of 4 doses, and durvalumab (1500 mg) via IV infusion every 4 weeks until disease progression

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

Dosage and administration details:

20 mg/mL, solution, IV

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

Dosage and administration details:

50 mg/mL, solution, IV

Arm title	Durvalumab
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Arm description:

durvalumab (1500 mg) via IV infusion every 4 weeks until disease progression

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

Dosage and administration details:

50 mg/mL, solution, IV

Arm title	Standard of Care (SOC)
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Arm description:

either cisplatin (at a dose of 100 mg/m² of body surface area as an IV infusion) or carboplatin (at an area under the concentration curve of 5 mg/mL/min as an IV infusion) on Day 1 of up to six 3-week cycles, and an infusion of 5-fluorouracil (5FU) (at a dose of 1000 mg/m²/day on Days 1 through 4) every 3 weeks, along with 400 mg/m² of cetuximab on Cycle 1 Day 1 and 250 mg/m² weekly for up to 6 cycles and maintenance cetuximab at 250 mg/m² administered via IV infusion weekly thereafter in patients who achieved stable disease (SD) or better upon completion of chemotherapy until disease progression, toxicity, or withdrawal of consent

Arm type	Active comparator
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV (as sourced locally)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV (as sourced locally)

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravesical solution/solution for injection, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV (as sourced locally)

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV (as sourced locally)

Number of subjects in period 1	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)
Started	413	204	206
Full analysis set	413	204	206
Safety analysis set	408	202	196
PD-L1 TC/IC high subgroup analysis set	190	99	94
Completed	0	0	0
Not completed	413	204	206
Adverse event, serious fatal	352	174	161
Consent withdrawn by subject	8	5	16

Patients alive or lost to follow-up at DCO	53	25	29
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Baseline characteristics

Reporting groups

Reporting group title	Durvalumab + tremelimumab
Reporting group description: tremelimumab (75 mg) via IV infusion every 4 weeks for a maximum of 4 doses, and durvalumab (1500 mg) via IV infusion every 4 weeks until disease progression	
Reporting group title	Durvalumab
Reporting group description: durvalumab (1500 mg) via IV infusion every 4 weeks until disease progression	
Reporting group title	Standard of Care (SOC)
Reporting group description: either cisplatin (at a dose of 100 mg/m ² of body surface area as an IV infusion) or carboplatin (at an area under the concentration curve of 5 mg/mL/min as an IV infusion) on Day 1 of up to six 3-week cycles, and an infusion of 5-fluorouracil (5FU) (at a dose of 1000 mg/m ² /day on Days 1 through 4) every 3 weeks, along with 400 mg/m ² of cetuximab on Cycle 1 Day 1 and 250 mg/m ² weekly for up to 6 cycles and maintenance cetuximab at 250 mg/m ² administered via IV infusion weekly thereafter in patients who achieved stable disease (SD) or better upon completion of chemotherapy until disease progression, toxicity, or withdrawal of consent	

Reporting group values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)
Number of subjects	413	204	206
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	265	132	133
From 65-84 years	146	71	73
85 years and over	2	1	0
Age Continuous Units: Years			
arithmetic mean	60.5	60.2	60.9
standard deviation	± 9.56	± 10.41	± 9.45
Sex: Female, Male Units: Participants			
Female	73	29	32
Male	340	175	174
Race/Ethnicity, Customized Units: Subjects			
White	298	145	160
Black or African American	5	3	2
Asian	109	54	42
Other	0	2	2
Missing	1	0	0

Reporting group values	Total		
Number of subjects	823		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	530		
From 65-84 years	290		
85 years and over	3		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	134		
Male	689		
Race/Ethnicity, Customized			
Units: Subjects			
White	603		
Black or African American	10		
Asian	205		
Other	4		
Missing	1		

End points

End points reporting groups

Reporting group title	Durvalumab + tremelimumab
Reporting group description: tremelimumab (75 mg) via IV infusion every 4 weeks for a maximum of 4 doses, and durvalumab (1500 mg) via IV infusion every 4 weeks until disease progression	
Reporting group title	Durvalumab
Reporting group description: durvalumab (1500 mg) via IV infusion every 4 weeks until disease progression	
Reporting group title	Standard of Care (SOC)
Reporting group description: either cisplatin (at a dose of 100 mg/m ² of body surface area as an IV infusion) or carboplatin (at an area under the concentration curve of 5 mg/mL/min as an IV infusion) on Day 1 of up to six 3-week cycles, and an infusion of 5-fluorouracil (5FU) (at a dose of 1000 mg/m ² /day on Days 1 through 4) every 3 weeks, along with 400 mg/m ² of cetuximab on Cycle 1 Day 1 and 250 mg/m ² weekly for up to 6 cycles and maintenance cetuximab at 250 mg/m ² administered via IV infusion weekly thereafter in patients who achieved stable disease (SD) or better upon completion of chemotherapy until disease progression, toxicity, or withdrawal of consent	

Primary: Overall Survival (OS) status in the PD-L1 TC/IC high subgroup - Durvalumab versus Standard of Care (SOC)

End point title	Overall Survival (OS) status in the PD-L1 TC/IC high subgroup - Durvalumab versus Standard of Care (SOC)
End point description: Number of participants with Overall Survival (OS)	
End point type	Primary
End point timeframe: From date of randomization until time of final analysis, an average of approximately 4 years	

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	99	94	
Units: Participants				
Death	162	84	77	
Voluntary Discontinuation by subject	1	1	3	
Alive or lost to follow up	27	14	14	

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Statistical analysis description: Statistical analysis of number of deaths	
Comparison groups	Durvalumab v Standard of Care (SOC)
Number of subjects included in analysis	193

Analysis specification	Pre-specified
Analysis type	
P-value	= 0.787 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.32

Notes:

[1] - 2 sided

Primary: Overall Survival (OS) median duration in the PD-L1 TC/IC high subgroup

End point title	Overall Survival (OS) median duration in the PD-L1 TC/IC high subgroup ^[2]
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End point description:

Time from the date of randomization until death due to any cause (i.e., date of death or censoring – date of randomization + 1)

End point type	Primary
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End point timeframe:

From date of randomization until time of final analysis, an average of approximately 4 years

Notes:

[2] - 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: The median duration of OS is presented with the associated 95% confidence interval, no further statistical analyses were performed.

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	99	94	
Units: Months				
median (confidence interval 95%)	11.2 (9.5 to 13.9)	10.9 (9.0 to 14.3)	10.9 (8.3 to 13.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) status in the PD-L1 TC/IC high subgroup - Durvalumab + tremelimumab versus Standard of Care (SOC)

End point title	Overall Survival (OS) status in the PD-L1 TC/IC high subgroup - Durvalumab + tremelimumab versus Standard of Care (SOC)
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End point description:

Number of participants with Overall Survival (OS)

End point type	Secondary
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End point timeframe:

From date of randomization until time of final analysis, an average of approximately 4 years

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	99	94	
Units: Participants				
Died	162	84	77	

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Durvalumab + tremelimumab v Standard of Care (SOC)
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.634 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.39

Notes:

[3] - 2 sided

Secondary: Percentage of patients alive at 12, 18 and 24 months in the PD-L1 TC/IC high subgroup

End point title	Percentage of patients alive at 12, 18 and 24 months in the PD-L1 TC/IC high subgroup
End point description:	
Percentage of patients alive	
End point type	Secondary
End point timeframe:	
12, 18 and 24 months after randomization	

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	99	94	
Units: % of participants				
number (confidence interval 95%)				

at 12 months	49.3 (42.0 to 56.2)	48.0 (37.8 to 57.4)	44.0 (33.6 to 53.8)	
at 18 months	31.8 (25.3 to 38.5)	34.7 (25.5 to 44.1)	30.8 (21.6 to 40.4)	
at 24 months	23.9 (18.0 to 30.1)	27.6 (19.2 to 36.6)	26.4 (17.8 to 35.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) in the PD-L1 TC/IC high subgroup

End point title	Progression Free Survival (PFS) in the PD-L1 TC/IC high subgroup
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End point description:

Time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression). Progression is defined using Response Evaluation Criteria in Solid Tumours criteria (RECIST v1.1), as $\geq 20\%$ increase in the sum of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions

End point type	Secondary
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End point timeframe:

Tumor assessments (per RECIST 1.1) every 6 weeks for the first 24 weeks relative to the date of randomization and then every 8 weeks thereafter, up to approximately 4 years

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	99	94	
Units: Months				
median (confidence interval 95%)	2.8 (2.6 to 3.3)	2.8 (1.7 to 4.2)	5.3 (4.3 to 5.8)	

Statistical analyses

Statistical analysis title	Progression Free Survival
Comparison groups	Durvalumab + tremelimumab v Standard of Care (SOC)
Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.028 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.76

Notes:

[4] - 2 sided

Statistical analysis title	Progression Free Survival
Comparison groups	Durvalumab v Standard of Care (SOC)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.287 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.8

Notes:

[5] - 2 sided

Secondary: Objective Response Rate (ORR) in the PD-L1 TC/IC high subgroup

End point title	Objective Response Rate (ORR) in the PD-L1 TC/IC high subgroup
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End point description:

Number (%) of patients with at least 1 visit response of complete response (CR) or partial response (PR). Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) for target lesions (TL) and assessed by MRI or CT: CR: Disappearance of all TLs since baseline; PR: $\geq 30\%$ decrease in the sum of diameters of TLs; Overall Response (OR = CR + PR)

End point type	Secondary
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End point timeframe:

Tumor assessments (per RECIST 1.1) every 6 weeks for the first 24 weeks relative to the date of randomization and then every 8 weeks thereafter, up to approximately 4 years

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	99	94	
Units: Participants				
Response	48	16	47	
No response	142	83	47	

Statistical analyses

Statistical analysis title	Objective Response Rate
Statistical analysis description:	
Statistical analysis of number with a response	
Comparison groups	Durvalumab + tremelimumab v Standard of Care (SOC)

Number of subjects included in analysis	284
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.57

Notes:

[6] - 2 sided

Statistical analysis title	Objective Response Rate
Statistical analysis description:	
Statistical analysis of number with a response	
Comparison groups	Durvalumab v Standard of Care (SOC)
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.37

Notes:

[7] - 2 sided

Secondary: Duration of Response (DoR) in the PD-L1 TC/IC high subgroup

End point title	Duration of Response (DoR) in the PD-L1 TC/IC high subgroup
End point description:	
Time from the date of first documented response until the first date of documented progression or death in the absence of disease progression	
End point type	Secondary
End point timeframe:	
Tumor assessments (per RECIST 1.1) every 6 weeks for the first 24 weeks relative to the date of randomization and then every 8 weeks thereafter, up to approximately 4 years	

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	16 ^[8]	47	
Units: Months				
median (confidence interval 95%)	6.5 (4.5 to 16.1)	12.3 (5.6 to 9999999999)	4.2 (3.0 to 5.7)	

Notes:

[8] - Upper confidence limit was not calculable due to insufficient participants with events.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) status in the all-comers (Full analysis set)

End point title	Overall Survival (OS) status in the all-comers (Full analysis set)
End point description:	
Number of participants with Overall Survival (OS)	
End point type	Secondary
End point timeframe:	
From date of randomization until time of final analysis, an average of approximately 4 years	

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	413	204	206	
Units: Participants				
Death	356	176	171	
Voluntary Discontinuation by subject	4	3	6	
Alive or lost to follow up	53	25	29	

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
Statistical analysis of number of deaths	
Comparison groups	Durvalumab v Standard of Care (SOC)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.811 ^[9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided

lower limit	0.83
upper limit	1.27

Notes:

[9] - 2 sided

Statistical analysis title	Overall Survival
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Statistical analysis description:

Statistical analysis of number of deaths

Comparison groups	Durvalumab + tremelimumab v Standard of Care (SOC)
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.624
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.25

Secondary: Overall Survival (OS) median duration in the all-comers (Full analysis set)

End point title	Overall Survival (OS) median duration in the all-comers (Full analysis set)
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End point description:

Time from the date of randomization until death due to any cause (i.e., date of death or censoring – date of randomization + 1)

End point type	Secondary
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End point timeframe:

From date of randomization until time of final analysis, an average of approximately 4 years

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	413	204	206	
Units: Months				
median (confidence interval 95%)	10.7 (9.6 to 12.2)	9.9 (8.9 to 11.9)	10.3 (9.0 to 12.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients alive at 12, 18 and 24 months in the all-comers (Full analysis set)

End point title	Percentage of patients alive at 12, 18 and 24 months in the all-comers (Full analysis set)
End point description: Percentage of patients alive	
End point type	Secondary
End point timeframe: 12, 18 and 24 months after randomization	

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	413	204	206	
Units: % of participants				
number (confidence interval 95%)				
at 12 months	46.5 (41.6 to 51.2)	42.8 (35.9 to 49.5)	43.8 (36.8 to 50.5)	
at 18 months	30.7 (26.3 to 35.2)	31.2 (24.9 to 37.7)	29.7 (23.5 to 36.1)	
at 24 months	22.9 (18.9 to 27.0)	24.7 (18.9 to 30.8)	23.2 (17.6 to 29.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) in the all-comers (Full analysis set)

End point title	Progression Free Survival (PFS) in the all-comers (Full analysis set)
End point description: Time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression). Progression is defined using Response Evaluation Criteria in Solid Tumours criteria (RECIST v1.1), as $\geq 20\%$ increase in the sum of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions	
End point type	Secondary
End point timeframe: Tumor assessments (per RECIST 1.1) every 6 weeks for the first 24 weeks relative to the date of randomization and then every 8 weeks thereafter, up to approximately 4 years	

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	413	204	206	
Units: Months				
median (confidence interval 95%)	2.8 (2.6 to 2.9)	2.8 (2.0 to 2.8)	5.4 (4.4 to 5.7)	

Statistical analyses

Statistical analysis title	Progression Free Survival
Comparison groups	Durvalumab v Standard of Care (SOC)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.006 ^[10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	1.68

Notes:

[10] - 2 sided

Statistical analysis title	Progression Free Survival
Comparison groups	Durvalumab + tremelimumab v Standard of Care (SOC)
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.008 ^[11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	1.53

Notes:

[11] - 2 sided

Secondary: Objective Response Rate (ORR) in the all-comers (Full analysis set)

End point title	Objective Response Rate (ORR) in the all-comers (Full analysis set)
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End point description:

Number (%) of patients with at least 1 visit response of complete response (CR) or partial response (PR). Per Response Evaluation Criteria in Solid Tumours (RECIST v1.1) for target lesions (TL) and

assessed by MRI or CT: CR: Disappearance of all TLs since baseline; PR: $\geq 30\%$ decrease in the sum of diameters of TLs; Overall Response (OR = CR + PR)

End point type	Secondary
End point timeframe:	
Tumor assessments (per RECIST 1.1) every 6 weeks for the first 24 weeks relative to the date of randomization and then every 8 weeks thereafter, up to approximately 4 years	

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	413	204	206	
Units: Participants				
Response	90	35	101	
No response	323	169	105	

Statistical analyses

Statistical analysis title	Objective Response Rate
Comparison groups	Durvalumab + tremelimumab v Standard of Care (SOC)
Number of subjects included in analysis	619
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.41

Notes:

[12] - 2 sided

Statistical analysis title	Objective Response Rate
Comparison groups	Durvalumab v Standard of Care (SOC)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 ^[13]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13

upper limit	0.33
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Notes:

[13] - 2 sided

Secondary: Duration of Response (DoR) in the all-comers (Full analysis set)

End point title	Duration of Response (DoR) in the all-comers (Full analysis set)
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End point description:

Time from the date of first documented response until the first date of documented progression or death in the absence of disease progression

End point type	Secondary
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End point timeframe:

Tumor assessments (per RECIST 1.1) every 6 weeks for the first 24 weeks relative to the date of randomization and then every 8 weeks thereafter, up to approximately 4 years

End point values	Durvalumab + tremelimumab	Durvalumab	Standard of Care (SOC)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	35	101	
Units: Months				
median (confidence interval 95%)	9.2 (6.0 to 19.6)	11.9 (4.6 to 17.8)	4.2 (3.7 to 4.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until last study visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Durvalumab + tremelimumab
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Reporting group description:

Durvalumab + tremelimumab

Reporting group title	Durvalamab
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Reporting group description:

Durvalamab

Reporting group title	Standard of Care (SOC)
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Reporting group description:

Standard of Care (SOC)

Serious adverse events	Durvalumab + tremelimumab	Durvalamab	Standard of Care (SOC)
Total subjects affected by serious adverse events			
subjects affected / exposed	168 / 408 (41.18%)	78 / 202 (38.61%)	94 / 196 (47.96%)
number of deaths (all causes)	352	174	161
number of deaths resulting from adverse events	38	21	21
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Hypotension			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 1
Orthostatic hypotension			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Vena cava thrombosis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Basal cell carcinoma			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Colorectal cancer			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
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 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Oesophageal carcinoma			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Prostate cancer			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Rectal cancer			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Tumour pain			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	5 / 408 (1.23%)	7 / 202 (3.47%)	0 / 196 (0.00%)

occurrences causally related to treatment / all	3 / 5	1 / 7	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	3 / 196 (1.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 408 (0.49%)	4 / 202 (1.98%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 2	1 / 4	0 / 2
Malaise			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Mucosal inflammation			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	4 / 196 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face oedema			
subjects affected / exposed	1 / 408 (0.25%)	3 / 202 (1.49%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			

subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Fatigue			
subjects affected / exposed	3 / 408 (0.74%)	2 / 202 (0.99%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oedema			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Pyrexia			
subjects affected / exposed	6 / 408 (1.47%)	3 / 202 (1.49%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	2 / 7	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Sudden death			
subjects affected / exposed	3 / 408 (0.74%)	1 / 202 (0.50%)	0 / 196 (0.00%)

occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 1	0 / 0
Soft tissue inflammation			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
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			
Adjustment disorder			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (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
Injury, poisoning and procedural complications			
Carbon monoxide poisoning			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Fall			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Gastrostomy failure			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Infusion related reaction			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Femoral neck fracture			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Post procedural fistula			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Post procedural haemorrhage			
subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (0.00%)

occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Blood glucose increased			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Lipase increased			
subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
White blood cell count decreased			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin T increased			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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 disorders			
Cardiac arrest			
subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Supraventricular tachycardia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 408 (0.00%)	2 / 202 (0.99%)	0 / 196 (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
Atrial fibrillation			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (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
Atrial flutter			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Cardiopulmonary failure			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Myocardial infarction			
subjects affected / exposed	1 / 408 (0.25%)	2 / 202 (0.99%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Tachycardia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Haemoptysis			
subjects affected / exposed	1 / 408 (0.25%)	3 / 202 (1.49%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Laryngeal stenosis			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (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
Pharyngeal oedema			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Pulmonary infarction			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Aspiration			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Bronchospasm			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (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
Dyspnoea			
subjects affected / exposed	4 / 408 (0.98%)	3 / 202 (1.49%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	1 / 5	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	2 / 408 (0.49%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung disorder			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Interstitial lung disease			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	5 / 408 (1.23%)	1 / 202 (0.50%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	3 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	5 / 408 (1.23%)	1 / 202 (0.50%)	4 / 196 (2.04%)
occurrences causally related to treatment / all	0 / 6	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Pleural effusion			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	5 / 196 (2.55%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pneumonitis			
subjects affected / exposed	7 / 408 (1.72%)	2 / 202 (0.99%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	9 / 9	2 / 2	2 / 2
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Respiratory distress			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Stridor			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	1 / 196 (0.51%)

occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper airway obstruction			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	3 / 196 (1.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Pancytopenia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	5 / 196 (2.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	8 / 196 (4.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	8 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	4 / 196 (2.04%)
occurrences causally related to	0 / 0	0 / 0	3 / 6

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	5 / 196 (2.55%)
occurrences causally related to treatment / all	1 / 1	1 / 1	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node haemorrhage			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	3 / 196 (1.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Cerebrovascular disorder			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Loss of consciousness			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Cerebral infarction			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (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
Ischaemic stroke			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (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
Encephalopathy			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Lethargy			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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

Syncope			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	3 / 196 (1.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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			
subjects affected / exposed	4 / 408 (0.98%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	9 / 408 (2.21%)	2 / 202 (0.99%)	4 / 196 (2.04%)
occurrences causally related to treatment / all	8 / 14	1 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (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
Enterocolitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Gastric haemorrhage			

subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Gastric ulcer perforation			
subjects affected / exposed	0 / 408 (0.00%)	2 / 202 (0.99%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Duodenal ulcer perforation			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	6 / 408 (1.47%)	1 / 202 (0.50%)	5 / 196 (2.55%)

occurrences causally related to treatment / all	0 / 6	0 / 1	1 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haematemesis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Intestinal haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Ileus paralytic			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Intestinal ischaemia			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (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
Large intestine perforation			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Mouth haemorrhage			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (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
Nausea			
subjects affected / exposed	5 / 408 (1.23%)	0 / 202 (0.00%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	2 / 5	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Pneumoperitoneum			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumatosis intestinalis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Proctitis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue oedema			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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

Upper gastrointestinal haemorrhage subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (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
Vomiting subjects affected / exposed	8 / 408 (1.96%)	1 / 202 (0.50%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	2 / 12	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders Autoimmune hepatitis subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (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
Hepatic function abnormal subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Hepatitis subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Hepatorenal failure subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Immune-mediated hepatitis subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 408 (0.49%)	1 / 202 (0.50%)	3 / 196 (1.53%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal failure			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	3 / 196 (1.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 408 (0.00%)	2 / 202 (0.99%)	0 / 196 (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
Skin ulcer			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Pemphigoid			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Psoriasis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Musculoskeletal and connective tissue disorders			
Autoimmune myositis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Musculoskeletal chest pain			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Osteonecrosis of jaw			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Arthralgia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Osteolysis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Back pain			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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

Trismus			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	3 / 196 (1.53%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Hyperkalaemia			
subjects affected / exposed	1 / 408 (0.25%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypokalaemia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Cachexia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Diabetic ketoacidosis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Hypocalcaemia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Hypoglycaemia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypomagnesaemia			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Hypophagia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Malnutrition			
subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Superinfection			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Oral infection			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Tracheitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Abdominal infection			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Acute sinusitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to	0 / 1	0 / 0	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess neck			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Bacterial sepsis			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
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 / 408 (0.25%)	1 / 202 (0.50%)	0 / 196 (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
Cellulitis			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	2 / 408 (0.49%)	1 / 202 (0.50%)	0 / 196 (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
Ear infection			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Escherichia urinary tract infection subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal infection subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Gastroenteritis subjects affected / exposed	2 / 408 (0.49%)	0 / 202 (0.00%)	0 / 196 (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
Gangrene subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Infection subjects affected / exposed	5 / 408 (1.23%)	0 / 202 (0.00%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection subjects affected / exposed	4 / 408 (0.98%)	1 / 202 (0.50%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mucosal infection			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Oesophageal candidiasis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Oral candidiasis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Parotitis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	2 / 408 (0.49%)	1 / 202 (0.50%)	0 / 196 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia			
subjects affected / exposed	32 / 408 (7.84%)	14 / 202 (6.93%)	13 / 196 (6.63%)
occurrences causally related to treatment / all	3 / 33	1 / 14	1 / 13
deaths causally related to treatment / all	0 / 4	0 / 3	0 / 4
Pyelonephritis			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Rash pustular			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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 tract infection bacterial subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory tract infection subjects affected / exposed	5 / 408 (1.23%)	2 / 202 (0.99%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Septic shock subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	2 / 196 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sepsis subjects affected / exposed	5 / 408 (1.23%)	1 / 202 (0.50%)	4 / 196 (2.04%)
occurrences causally related to treatment / all	0 / 5	0 / 1	3 / 4
deaths causally related to treatment / all	0 / 3	0 / 0	1 / 1
Skin infection subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Staphylococcal infection subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	0 / 196 (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
Tracheobronchitis subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Wound infection			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	0 / 196 (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
Viral infection			
subjects affected / exposed	0 / 408 (0.00%)	0 / 202 (0.00%)	1 / 196 (0.51%)
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	Durvalumab	Standard of Care (SOC)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	317 / 408 (77.70%)	153 / 202 (75.74%)	182 / 196 (92.86%)
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 408 (6.62%)	9 / 202 (4.46%)	11 / 196 (5.61%)
occurrences (all)	36	10	19
Hypotension			
subjects affected / exposed	11 / 408 (2.70%)	5 / 202 (2.48%)	11 / 196 (5.61%)
occurrences (all)	15	5	16
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	66 / 408 (16.18%)	35 / 202 (17.33%)	56 / 196 (28.57%)
occurrences (all)	74	41	68
Asthenia			
subjects affected / exposed	52 / 408 (12.75%)	18 / 202 (8.91%)	38 / 196 (19.39%)
occurrences (all)	60	23	61
Mucosal inflammation			
subjects affected / exposed	15 / 408 (3.68%)	6 / 202 (2.97%)	43 / 196 (21.94%)
occurrences (all)	16	8	58
Pyrexia			
subjects affected / exposed	48 / 408 (11.76%)	12 / 202 (5.94%)	21 / 196 (10.71%)
occurrences (all)	54	13	33

Psychiatric disorders			
Insomnia			
subjects affected / exposed	29 / 408 (7.11%)	8 / 202 (3.96%)	11 / 196 (5.61%)
occurrences (all)	31	9	11
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	27 / 408 (6.62%)	8 / 202 (3.96%)	11 / 196 (5.61%)
occurrences (all)	37	10	14
Lipase increased			
subjects affected / exposed	21 / 408 (5.15%)	5 / 202 (2.48%)	2 / 196 (1.02%)
occurrences (all)	27	8	2
Neutrophil count decreased			
subjects affected / exposed	0 / 408 (0.00%)	1 / 202 (0.50%)	24 / 196 (12.24%)
occurrences (all)	0	1	36
Platelet count decreased			
subjects affected / exposed	5 / 408 (1.23%)	1 / 202 (0.50%)	22 / 196 (11.22%)
occurrences (all)	5	1	47
Weight decreased			
subjects affected / exposed	39 / 408 (9.56%)	13 / 202 (6.44%)	26 / 196 (13.27%)
occurrences (all)	42	15	32
Alanine aminotransferase increased			
subjects affected / exposed	23 / 408 (5.64%)	6 / 202 (2.97%)	14 / 196 (7.14%)
occurrences (all)	26	6	18
Blood creatinine increased			
subjects affected / exposed	15 / 408 (3.68%)	3 / 202 (1.49%)	12 / 196 (6.12%)
occurrences (all)	20	4	19
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	61 / 408 (14.95%)	22 / 202 (10.89%)	65 / 196 (33.16%)
occurrences (all)	68	26	97
Leukopenia			
subjects affected / exposed	2 / 408 (0.49%)	2 / 202 (0.99%)	26 / 196 (13.27%)
occurrences (all)	2	3	48
Neutropenia			

subjects affected / exposed occurrences (all)	2 / 408 (0.49%) 2	0 / 202 (0.00%) 0	63 / 196 (32.14%) 103
Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 408 (1.47%) 24	0 / 202 (0.00%) 0	39 / 196 (19.90%) 76
Respiratory, thoracic and mediastinal disorders			
Productive cough subjects affected / exposed occurrences (all)	19 / 408 (4.66%) 22	12 / 202 (5.94%) 12	5 / 196 (2.55%) 5
Cough subjects affected / exposed occurrences (all)	44 / 408 (10.78%) 47	14 / 202 (6.93%) 14	13 / 196 (6.63%) 15
Dyspnoea subjects affected / exposed occurrences (all)	34 / 408 (8.33%) 40	5 / 202 (2.48%) 5	18 / 196 (9.18%) 21
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	15 / 408 (3.68%) 18	7 / 202 (3.47%) 7	14 / 196 (7.14%) 15
Headache subjects affected / exposed occurrences (all)	29 / 408 (7.11%) 35	11 / 202 (5.45%) 12	13 / 196 (6.63%) 13
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	70 / 408 (17.16%) 113	15 / 202 (7.43%) 20	60 / 196 (30.61%) 96
Constipation subjects affected / exposed occurrences (all)	59 / 408 (14.46%) 72	24 / 202 (11.88%) 25	54 / 196 (27.55%) 68
Dysphagia subjects affected / exposed occurrences (all)	26 / 408 (6.37%) 28	8 / 202 (3.96%) 9	4 / 196 (2.04%) 4
Nausea subjects affected / exposed occurrences (all)	52 / 408 (12.75%) 65	13 / 202 (6.44%) 14	74 / 196 (37.76%) 120
Stomatitis			

subjects affected / exposed	14 / 408 (3.43%)	6 / 202 (2.97%)	40 / 196 (20.41%)
occurrences (all)	16	6	54
Vomiting			
subjects affected / exposed	34 / 408 (8.33%)	8 / 202 (3.96%)	39 / 196 (19.90%)
occurrences (all)	52	9	66
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 408 (0.74%)	0 / 202 (0.00%)	11 / 196 (5.61%)
occurrences (all)	3	0	11
Dermatitis acneiform			
subjects affected / exposed	2 / 408 (0.49%)	2 / 202 (0.99%)	36 / 196 (18.37%)
occurrences (all)	2	2	50
Dry skin			
subjects affected / exposed	23 / 408 (5.64%)	4 / 202 (1.98%)	26 / 196 (13.27%)
occurrences (all)	24	4	34
Skin fissures			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	18 / 196 (9.18%)
occurrences (all)	1	0	23
Pruritus			
subjects affected / exposed	45 / 408 (11.03%)	11 / 202 (5.45%)	17 / 196 (8.67%)
occurrences (all)	61	13	18
Rash			
subjects affected / exposed	50 / 408 (12.25%)	17 / 202 (8.42%)	81 / 196 (41.33%)
occurrences (all)	62	17	114
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	23 / 408 (5.64%)	8 / 202 (3.96%)	3 / 196 (1.53%)
occurrences (all)	27	8	5
Pain in extremity			
subjects affected / exposed	5 / 408 (1.23%)	5 / 202 (2.48%)	10 / 196 (5.10%)
occurrences (all)	6	5	10
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	23 / 408 (5.64%)	6 / 202 (2.97%)	0 / 196 (0.00%)
occurrences (all)	30	6	0
Hypothyroidism			

subjects affected / exposed occurrences (all)	68 / 408 (16.67%) 79	21 / 202 (10.40%) 23	7 / 196 (3.57%) 7
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	7 / 408 (1.72%)	0 / 202 (0.00%)	16 / 196 (8.16%)
occurrences (all)	7	0	27
Decreased appetite			
subjects affected / exposed	52 / 408 (12.75%)	20 / 202 (9.90%)	46 / 196 (23.47%)
occurrences (all)	57	22	59
Hyponatraemia			
subjects affected / exposed	26 / 408 (6.37%)	2 / 202 (0.99%)	11 / 196 (5.61%)
occurrences (all)	30	4	14
Hypomagnesaemia			
subjects affected / exposed	11 / 408 (2.70%)	3 / 202 (1.49%)	45 / 196 (22.96%)
occurrences (all)	11	6	77
Hypokalaemia			
subjects affected / exposed	21 / 408 (5.15%)	6 / 202 (2.97%)	22 / 196 (11.22%)
occurrences (all)	26	8	42
Hyperglycaemia			
subjects affected / exposed	29 / 408 (7.11%)	6 / 202 (2.97%)	8 / 196 (4.08%)
occurrences (all)	37	8	10
Dehydration			
subjects affected / exposed	8 / 408 (1.96%)	0 / 202 (0.00%)	10 / 196 (5.10%)
occurrences (all)	10	0	11
Infections and infestations			
Paronychia			
subjects affected / exposed	1 / 408 (0.25%)	0 / 202 (0.00%)	21 / 196 (10.71%)
occurrences (all)	1	0	24
Pneumonia			
subjects affected / exposed	19 / 408 (4.66%)	7 / 202 (3.47%)	10 / 196 (5.10%)
occurrences (all)	22	7	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2016	The text has been updated to reflect that BICR assessments according to RECIST 1.1 will be used instead of Investigator assessments to measure the co-primary objective of PFS and the secondary objectives of PFS, ORR, DoR, and APF12
13 February 2018	Change of Progression Free Survival from primary objective to secondary objective
03 October 2018	Change of Overall Survival in the all-comer population from primary objective to secondary objective
25 January 2019	Change of primary objective from MEDI4736 + tremelimumab combination therapy versus SoC in a biomarker-selected subgroup (PD-L1 TC/IC), to MEDI4736 monotherapy versus SoC in all randomized patients (all-comers) in terms of OS
04 October 2019	Change of primary objective from MEDI4736 monotherapy versus SoC in all randomized patients (all-comers) in terms of OS to MEDI4736 monotherapy versus SoC in patients who are at low risk of early mortality based on baseline characteristics in terms of OS
29 June 2020	Change of primary objective from MEDI4736 monotherapy versus Standard of Care (SoC) in patients who are at low risk of early mortality based on baseline laboratory values according to a model developed by AstraZeneca in terms of SoC, to MEDI4736 versus SoC in a biomarker-selected population (PD-L1 TC/IC high subgroup) in terms of overall survival (OS)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported