Clinical trial results:
A Phase III, Open-label, Randomized, Multi-center, International Study of MEDI4736, Given as Monotherapy or in Combination with Tremelimumab, Determined by PD-L1 Expression, Versus Standard of Care in Patients with Locally Advanced or Metastatic Non-small Cell Lung Cancer (Stage IIIB-IV) Who Have Received At Least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen and Do Not Have Known EGFR TK Activating Mutations or ALK Rearrangements (ARCTIC)

Summary

EudraCT number	2014-000338-46
Trial protocol	DE GB ES BE GR HU NL CZ PL IT
Global end of trial date	30 August 2023

Results information

Result version number	v1 (current)
This version publication date	10 August 2024
First version publication date	10 August 2024

Trial information

Trial identification

Sponsor protocol code	D4191C00004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02352948
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Alderley Park, Macclesfield, Cheshire, United Kingdom, SK10 4TG
Public contact	Medical Science Director, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2018
Global end of trial reached?	Yes
Global end of trial date	30 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Sub-study A [Programmed cell death ligand 1 (PD-L1) high population]: To assess the efficacy of durvalumab monotherapy compared with standard of care (SoC) in terms of overall survival (OS) and progression-free survival (PFS).
Sub-study B (PD-L1 low/neg population): To assess the efficacy of durvalumab in combination with tremelimumab treatment compared with SoC in terms of OS and PFS.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 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	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 48
Country: Number of subjects enrolled	Japan: 112
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Korea, Republic of: 29

Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	Spain: 64
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 55
Worldwide total number of subjects	595
EEA total number of subjects	282

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)	318
From 65 to 84 years	277
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was divided into 2 parts, sub-study A (82 centers across Europe, Asia, and North America) and sub-study B (149 centers across Europe, Asia, North America, and South America) conducted between 13 January 2015 and 09 February 2018 (data cut-off date).

Pre-assignment

Screening details:

The study had a pre-screening period to determine the programmed cell death ligand 1 (PD-L1) status, followed by a screening period and 12 month treatment period. A total of 595 participants were randomized to either sub-study A [PD-L1 high (>=25% of tumor cell (TC) expressing PD-L1)] or sub-study B [PD-L1 low/neg (<25% of TC expressing PD-L1)].

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sub-study A: Durvalumab

Arm description:

Participants received durvalumab 10 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (Q2W) for 12 months (up to 26 doses).

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

Dosage and administration details:

Durvalumab 10 mg/kg IV infusion Q2W for 12 months.

Arm title	Sub-study A: SoC

Arm description:

Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/meter square (m^2) IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until progression of disease (PD), initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.

Arm type	Active comparator
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib 150 mg orally once daily.

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Vinorelbine 30 mg/m^2 IV on Days 1, 8, 15, and 22 of a 28-day cycle.

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

Dosage and administration details:

Gemcitabine 1000 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle.

Arm title	Sub-study B: Durvalumab+Tremelimumab

Arm description:

Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion every 4 weeks (Q4W) for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses).

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

Dosage and administration details:

Tremelimumab 1 mg/kg IV infusion Q4W for 12 weeks.

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

Dosage and administration details:

Durvalumab 20 mg/kg IV infusion Q4W for 12 weeks followed by durvalumab 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16.

Arm title	Sub-study B: SoC

Arm description:

Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.

Arm type	Active comparator
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib 150 mg orally once daily.

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

Dosage and administration details:

Gemcitabine 1000 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle.

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

Dosage and administration details:

Vinorelbine 30 mg/m^2 IV on Days 1, 8, 15, and 22 of a 28-day cycle.

Arm title	Sub-study B: Durvalumab

Arm description:

Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).

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

Dosage and administration details:

Durvalumab 10 mg/kg IV infusion Q2W for 12 months.

Arm title	Sub-study B: Tremelimumab

Arm description:

Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by every 12 weeks (Q12W) for 24 weeks (up to 9 doses).

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

Dosage and administration details:

Tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by Q12W for 24 weeks.

Number of subjects in period 1	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab
Started	62	64	174
Received treatment	62	63	173
Completed study treatment	15	0 [1]	36 [2]
Completed	13	5	45
Not completed	49	59	129
Adverse event, serious fatal	47	48	114
Consent withdrawn by subject	1	10	11
Eligibility criteria not fulfilled	-	1	-
Unspecified	-	-	2
Lost to follow-up	1	-	2

Number of subjects in period 1	Sub-study B: SoC	Sub-study B: Durvalumab	Sub-study B: Tremelimumab

Started	118	117	60
Received treatment	110	117	60
Completed study treatment	0 [3]	23 [4]	4 [5]
Completed	19	29	11
Not completed	99	88	49
Adverse event, serious fatal	74	77	44
Consent withdrawn by subject	23	9	4
Eligibility criteria not fulfilled	1	-	-
Unspecified	-	-	-
Lost to follow-up	1	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

Baseline characteristics

Reporting groups	
Reporting group title	Sub-study A: Durvalumab
Reporting group description:	
Participants received durvalumab 10 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (Q2W) for 12 months (up to 26 doses).	
Reporting group title	Sub-study A: SoC
Reporting group description:	
Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/meter square (m^2) IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until progression of disease (PD), initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.	
Reporting group title	Sub-study B: Durvalumab+Tremelimumab
Reporting group description:	
Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion every 4 weeks (Q4W) for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses).	
Reporting group title	Sub-study B: SoC
Reporting group description:	
Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.	
Reporting group title	Sub-study B: Durvalumab
Reporting group description:	
Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).	
Reporting group title	Sub-study B: Tremelimumab
Reporting group description:	
Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by every 12 weeks (Q12W) for 24 weeks (up to 9 doses).	

Reporting group values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab
Number of subjects	62	64	174
Age, Customized Units: Subjects			
<50 years	3	11	16
>=50 to <65 years	31	25	79
>=65 to <75 years	24	21	64
>=75 years	4	7	15
Sex: Female, Male Units: Subjects			
Female	20	16	59
Male	42	48	115
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	22	23	41
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	0	1	3
White	40	40	129
Unknown or Not Reported	0	0	0
Other	0	0	1

Reporting group values	Sub-study B: SoC	Sub-study B: Durvalumab	Sub-study B: Tremelimumab
Number of subjects	118	117	60
Age, Customized Units: Subjects			
<50 years	8	13	4
>=50 to <65 years	49	52	27
>=65 to <75 years	50	39	24
>=75 years	11	13	5
Sex: Female, Male Units: Subjects			
Female	37	44	21
Male	81	73	39
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	41	34	16
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	1
White	74	79	43
Unknown or Not Reported	0	1	0
Other	1	1	0

Reporting group values	Total		
Number of subjects	595		
Age, Customized Units: Subjects			
<50 years	55		
>=50 to <65 years	263		
>=65 to <75 years	222		
>=75 years	55		
Sex: Female, Male Units: Subjects			
Female	197		
Male	398		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0		
Asian	177		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	9		
White	405		
Unknown or Not Reported	1		
Other	3		

End points

End points reporting groups

Reporting group title	Sub-study A: Durvalumab
Reporting group description:	
Participants received durvalumab 10 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (Q2W) for 12 months (up to 26 doses).	
Reporting group title	Sub-study A: SoC
Reporting group description:	
Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/meter square (m^2) IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until progression of disease (PD), initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.	
Reporting group title	Sub-study B: Durvalumab+Tremelimumab
Reporting group description:	
Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion every 4 weeks (Q4W) for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses).	
Reporting group title	Sub-study B: SoC
Reporting group description:	
Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.	
Reporting group title	Sub-study B: Durvalumab
Reporting group description:	
Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).	
Reporting group title	Sub-study B: Tremelimumab
Reporting group description:	
Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by every 12 weeks (Q12W) for 24 weeks (up to 9 doses).	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]
End point description:	
The OS was defined as the time from the date of randomization until death due to any cause. Sub-study A and B: Full analysis set (FAS) included all randomized participants analyzed on an intent-to-treat (ITT) basis.	
End point type	Primary
End point timeframe:	
From randomization (Day 1) until death due to any cause, approximately 36 months	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: no statistical analyses performed

End point values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	64	174	118
Units: months				
median (confidence interval 95%)	11.7 (8.2 to 17.4)	6.8 (4.9 to 10.2)	11.5 (8.7 to 14.1)	8.7 (6.5 to 11.7)

Statistical analyses

Statistical analysis title	Sub-study A: Durvalumab Vs SoC
Statistical analysis description:	
For sub-study A: durvalumab monotherapy treatment arm was compared with SoC.	
Comparison groups	Sub-study A: SoC v Sub-study A: Durvalumab
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.93

Notes:

[2] - Sub-study A was not powered and thus no formal statistical comparisons were performed. Hazard ratio and confidence interval (CI) are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs SoC
Statistical analysis description:	
For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC.	
Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.109 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.05

Notes:

[3] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and
histology in strata statement, and CI is calculated using profile likelihood approach.

[4] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[5]

End point description:

The PFS was defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdrew from randomized therapy or received another anti-cancer therapy prior to progression. The PFS was determined by Investigator assessments according to response evaluation criteria in solid tumours (RECIST) version 1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 millimeter (mm) or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis.

End point type	Primary

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: no statistical analyses performed

End point values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	64	174	118
Units: months				
median (confidence interval 95%)	3.8 (1.9 to 5.6)	2.2 (1.9 to 3.7)	3.5 (2.3 to 4.6)	3.5 (1.9 to 3.9)

Statistical analyses

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs SoC

Statistical analysis description:

For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.056 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.01

Notes:

[6] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and
histology in strata statement, and CI is calculated using profile likelihood approach.

[7] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Statistical analysis title	Sub-study A: Durvalumab Vs SoC
Statistical analysis description:	
For sub-study A: durvalumab monotherapy treatment arm was compared with SoC.	
Comparison groups	Sub-study A: Durvalumab v Sub-study A: SoC
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.04

Notes:

[8] - Sub-study A was not powered and thus no formal statistical comparisons were performed. Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

Secondary: OS, Contribution of the Components Analysis of Sub-study B

End point title	OS, Contribution of the Components Analysis of Sub-study B[9]
End point description:	
The OS was defined as the time from the date of randomization until death due to any cause. The FAS included all randomized participants analyzed on an ITT basis.	
End point type	Secondary
End point timeframe:	
From randomization (Day 1) until death due to any cause, approximately 36 months	

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: no statistical analyses performed

End point values	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: Durvalumab	Sub-study B: Tremelimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	117	60	
Units: months				
median (confidence interval 95%)	11.5 (8.7 to 14.1)	10.0 (7.1 to 13.2)	6.9 (3.9 to 13.2)	

Statistical analyses

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs Durvalumab
Statistical analysis description:	
As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with durvalumab monotherapy.	
Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B:

	Durvalumab
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.885 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.3

Notes:

[10] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and
histology in strata statement, and CI is calculated using profile likelihood approach.
[11] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Statistical analysis title	Sub-study B: Durvalumab+TremelimumabVsTremelimumab

Statistical analysis description:

As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with tremelimumab monotherapy.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Tremelimumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.153 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.11

Notes:

[12] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and
histology in strata statement, and CI is calculated using profile likelihood approach.
[13] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Secondary: Percentage of Participants Alive at 12 Months (OS12)

End point title	Percentage of Participants Alive at 12 Months (OS12)

End point description:

The OS12 was defined as the percentage of participants who were alive at 12 months after randomisation per Kaplan-Meier estimate of OS at 12 months. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

From randomization (Day 1) up to 12 months

End point values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	64	174	118
Units: percentage of participants				
number (confidence interval 95%)	49.3 (36.3 to 61.0)	31.3 (20.2 to 43.0)	49.5 (41.7 to 56.7)	38.8 (29.9 to 47.7)

End point values	Sub-study B: Durvalumab	Sub-study B: Tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	60		
Units: percentage of participants				
number (confidence interval 95%)	43.6 (34.4 to 52.4)	41.2 (28.7 to 53.3)		

Statistical analyses

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs SoC

Statistical analysis description:

For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.063 [15]
Method	z-test

Notes:

[14] - The variance is estimated using the delta method and Greenwood's formula.

[15] - The z-test statistic is the ratio of log-transformed ratio of the cumulative hazards in the 2 treatment arms divided by square root of the variance.

Secondary: PFS, Contribution of the Components Analysis of Sub-study B

End point title	PFS, Contribution of the Components Analysis of Sub-study

End point description:

The PFS was defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdrew from randomized therapy or received another anti-cancer therapy prior to progression. The PFS was determined by Investigator assessments according to RECIST v1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. FAS included all randomized participants analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks

thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: no statistical analyses performed

End point values	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: Durvalumab	Sub-study B: Tremelimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	117	60	
Units: months				
median (confidence interval 95%)	3.5 (2.3 to 4.6)	3.1 (1.9 to 3.7)	2.1 (1.8 to 3.2)	

Statistical analyses

Statistical analysis title	Sub-study B: Durvalumab+TremelimumabVsTremelimumab

Statistical analysis description:

As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with tremelimumab monotherapy.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Tremelimumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.011 [18]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.92

Notes:

[17] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and
histology in strata statement, and CI is calculated using profile likelihood approach.
[18] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs Durvalumab

Statistical analysis description:

As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with durvalumab monotherapy.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Durvalumab

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.282 [20]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.12

Notes:

[19] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and
histology in strata statement, and CI is calculated using profile likelihood approach.
[20] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR was defined as the percentage of participants with at least 1 visit response of complete response (CR) or partial response (PR) among ITT participants who had measurable disease at baseline. CR was defined as disappearance of all target lesions (any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm) and PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum of diameters as long as criteria for PD are not met). The ORR was measured using Investigator assessments according to RECIST v1.1. Sub-study A and B: FAS included all randomized participants with measureable disease at baseline analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

End point values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	64	174	118
Units: percentage of participants				
number (not applicable)	35.5	12.5	14.9	6.8

End point values	Sub-study B: Durvalumab	Sub-study B: Tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	60		
Units: percentage of participants				
number (not applicable)	15.4	6.7		

Statistical analyses

Statistical analysis title	Sub-study A: Durvalumab Vs SoC
Statistical analysis description:	
For sub-study A: durvalumab monotherapy treatment arm was compared with SoC.	
Comparison groups	Sub-study A: Durvalumab v Sub-study A: SoC
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[21]
Parameter estimate	Odds ratio (OR)
Point estimate	3.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	10.1

Notes:

[21] - Sub-study A was not powered and thus no formal statistical comparisons were performed. The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib)
and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

Statistical analysis title	Sub-study B: Durvalumab+TremelimumabVsTremelimumab
Statistical analysis description:	
For sub-study B: durvalumab plus tremelimumab treatment arm was compared with tremelimumab monotherapy.	
Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Tremelimumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.109
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	8.61

Notes:

[22] - The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs Durvalumab
Statistical analysis description:	
For sub-study B: durvalumab plus tremelimumab treatment arm was compared with durvalumab	

monotherapy.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Durvalumab
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.923
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.89

Notes:

[23] - The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs SoC

Statistical analysis description:

For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.037
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	5.94

Notes:

[24] - The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

The DoR was defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The DoR was determined by Investigator assessments according to RECIST v1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants with measureable disease at baseline analyzed on an ITT basis. Only participants with objective response were analyzed. Here, '99999' denotes 'upper limit of 75th percentile was not reached'.

End point type	Secondary

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

End point values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	8	26	8
Units: months				
median (inter-quartile range (Q1-Q3))	9.5 (3.0 to 17.8)	4.8 (1.9 to 7.6)	12.2 (6.5 to 99999)	10.8 (5.6 to 12.2)

End point values	Sub-study B: Durvalumab	Sub-study B: Tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	4		
Units: months				
median (inter-quartile range (Q1-Q3))	10.0 (4.0 to 99999)	4.7 (2.9 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive and Progression Free at 6 Months (APF6)

End point title	Percentage of Participants Alive and Progression Free at 6 Months (APF6)

End point description:

The APF6 was defined as the percentage of participants who were alive and progression free per RECIST v1.1 at 6 months after randomization per Kaplan-Meier estimate of PFS at 6 months. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 6 months

End point values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	64	174	118
Units: percentage of participants				
number (confidence interval 95%)	35.5 (23.9 to 47.3)	24.1 (14.1 to 35.6)	31.5 (24.6 to 38.7)	27.6 (19.0 to 36.7)

End point values	Sub-study B: Durvalumab	Sub-study B: Tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	60		
Units: percentage of participants				
number (confidence interval 95%)	27.2 (19.4 to 35.6)	14.5 (6.9 to 24.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive and Progression Free at 12 Months (APF12)

End point title	Percentage of Participants Alive and Progression Free at 12 Months (APF12)

End point description:

The APF12 was defined as the percentage of participants who were alive and progression free per RECIST v1.1 at 12 months after randomization per Kaplan-Meier estimate of PFS at 12 months. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 12 months.

End point values	Sub-study A: Durvalumab	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	64	174	118
Units: percentage of participants				
number (confidence interval 95%)	19.4 (10.7 to 30.0)	9.9 (3.8 to 19.3)	20.6 (14.7 to 27.1)	8.0 (3.4 to 15.2)

End point values	Sub-study B: Durvalumab	Sub-study B: Tremelimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	60		
Units: percentage of participants				
number (confidence interval 95%)	15.0 (9.1 to 22.3)	7.3 (2.4 to 16.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Randomisation to Second Progression (PFS2) of Sub-study B

End point title	Time From Randomisation to Second Progression (PFS2) of Sub-study B[25]

End point description:

The PFS2 was defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death and determined by local standard clinical practice and have included any of the following: objective radiological, symptomatic progression, or death. PFS2 was reported for sub-study B only. The FAS included all randomized participants analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until first progression. Disease then assessed per local practice until 2nd progression. Assessed up to a maximum of approximately 3 years.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: no statistical analyses performed

End point values	Sub-study B: Durvalumab+Tremelimumab	Sub-study B: SoC	Sub-study B: Durvalumab	Sub-study B: Tremelimumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	174	118	117	60
Units: months				
median (confidence interval 95%)	9.1 (6.6 to 12.3)	6.7 (4.7 to 8.9)	8.0 (6.3 to 10.0)	5.7 (3.2 to 10.0)

Statistical analyses

Statistical analysis title	Sub-study B: Durvalumab+Tremelimumab Vs SoC

Statistical analysis description:

For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC.

Comparison groups	Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.002 [27]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.85

Notes:

[26] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and
histology in strata statement, and CI is calculated using profile likelihood approach.

[27] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent up to 90 days after the last dose of durvalumab and/or tremelimumab and 30 days after the last dose of SoC, approximately 15 months.

Adverse event reporting additional description:

Sub-study A and B: Safety analysis set included all participants who received at least 1 dose of randomized treatment. Total # of deaths (all causes) was defined as death due to any cause (including disease progression) for the entire duration of the study assessed in all randomised participants.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Sub-study A: SoC

Reporting group description:

Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.

Reporting group title	Sub-study B: Durvalumab+Tremelimumab

Reporting group description:

Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion Q4W for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses).

Reporting group title	Sub-study A: Durvalumab

Reporting group description:

Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).

Reporting group title	Sub-study B: SoC

Reporting group description:

Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m^2 IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.

Reporting group title	Sub-study B: Tremelimumab

Reporting group description:

Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by Q12W for 24 weeks (up to 9 doses).

Reporting group title	Sub-study B: Durvalumab

Reporting group description:

Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).

Serious adverse events	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study A: Durvalumab
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 63 (25.40%)	65 / 173 (37.57%)	23 / 62 (37.10%)
number of deaths (all causes)	55	118	48
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Tumour necrosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage IV			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Pelvic venous thrombosis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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

Internal haemorrhage			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Hypotension			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Superior vena cava syndrome			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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

Asthenia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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	1 / 63 (1.59%)	1 / 173 (0.58%)	0 / 62 (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
General physical health deterioration			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Hyperthermia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Perforation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Sudden cardiac death			
subjects affected / exposed	0 / 63 (0.00%)	2 / 173 (1.16%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 63 (0.00%)	7 / 173 (4.05%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	2 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 63 (1.59%)	2 / 173 (1.16%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 63 (0.00%)	5 / 173 (2.89%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1

Acute respiratory failure			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchial fistula			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 63 (0.00%)	2 / 173 (1.16%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 63 (0.00%)	2 / 173 (1.16%)	0 / 62 (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
Interstitial lung disease			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 63 (0.00%)	2 / 173 (1.16%)	3 / 62 (4.84%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 63 (0.00%)	5 / 173 (2.89%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Transaminases increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
C-reactive protein increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Blood creatinine increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Injury, poisoning and procedural complications			
Overdose			

subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured ischium			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Atrial fibrillation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Cardiac arrest			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 63 (0.00%)	2 / 173 (1.16%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Cardiac failure congestive			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Tachycardia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Vocal cord paralysis			

subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Epilepsy			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Transient ischaemic attack			

subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 173 (0.00%)	0 / 62 (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
Febrile neutropenia			
subjects affected / exposed	5 / 63 (7.94%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Pancytopenia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Dysphagia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 63 (0.00%)	3 / 173 (1.73%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 63 (0.00%)	3 / 173 (1.73%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	3 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Vomiting			
subjects affected / exposed	0 / 63 (0.00%)	3 / 173 (1.73%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Ileus paralytic			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	0 / 63 (0.00%)	3 / 173 (1.73%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			

subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Haematuria			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
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 kidney injury			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Renal failure			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Glucocorticoid deficiency			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Inappropriate antidiuretic hormone			

secretion			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 63 (0.00%)	2 / 173 (1.16%)	0 / 62 (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
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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 infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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

Appendicitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Bronchitis viral			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Infectious pleural effusion			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	0 / 62 (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
Pneumocystis jirovecii pneumonia			

subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 63 (4.76%)	7 / 173 (4.05%)	4 / 62 (6.45%)
occurrences causally related to treatment / all	1 / 3	1 / 7	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pulmonary sepsis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 63 (1.59%)	1 / 173 (0.58%)	0 / 62 (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
Respiratory tract infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Varicella zoster virus infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Hypercalcaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 173 (0.58%)	0 / 62 (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
Hyperglycaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 173 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Sub-study B: SoC	Sub-study B: Tremelimumab	Sub-study B: Durvalumab
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 110 (25.45%)	23 / 60 (38.33%)	36 / 117 (30.77%)
number of deaths (all causes)	90	46	83
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colorectal cancer			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (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
Cancer pain			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour necrosis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage IV			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Subclavian vein thrombosis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Shock haemorrhagic			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			

subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
General physical health deterioration			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforation			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			

subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 110 (1.82%)	0 / 60 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 110 (0.91%)	1 / 60 (1.67%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Bronchial fistula			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 110 (0.00%)	2 / 60 (3.33%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 110 (0.91%)	2 / 60 (3.33%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	1 / 1
Psychiatric disorders			

Mental status changes			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			

subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured ischium			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Atrial fibrillation			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Angina pectoris			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Cardiac failure			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			

subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (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
Ischaemic stroke			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Epilepsy			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (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
Syncope			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 110 (0.91%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Pancytopenia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Dysphagia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 110 (0.00%)	7 / 60 (11.67%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	7 / 8	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	0 / 110 (0.00%)	5 / 60 (8.33%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Ascites			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal toxicity			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (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
Abdominal pain			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Vomiting			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			

subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucocorticoid deficiency			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thyroiditis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Back pain			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 110 (0.00%)	2 / 60 (3.33%)	0 / 117 (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
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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

Bronchitis viral			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
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	0 / 110 (0.00%)	1 / 60 (1.67%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infection			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (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
Influenza			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 110 (1.82%)	2 / 60 (3.33%)	2 / 117 (1.71%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster virus infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	0 / 117 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			

subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	0 / 117 (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
Hypercalcaemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 110 (0.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
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	Sub-study A: SoC	Sub-study B: Durvalumab+Tremelimumab	Sub-study A: Durvalumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 63 (93.65%)	139 / 173 (80.35%)	52 / 62 (83.87%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	4 / 63 (6.35%)	2 / 173 (1.16%)	2 / 62 (3.23%)
occurrences (all)	4	3	2
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 63 (3.17%)	11 / 173 (6.36%)	1 / 62 (1.61%)
occurrences (all)	2	12	2
Alanine aminotransferase increased			

subjects affected / exposed	3 / 63 (4.76%)	10 / 173 (5.78%)	1 / 62 (1.61%)
occurrences (all)	3	11	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 63 (3.17%)	4 / 173 (2.31%)	4 / 62 (6.45%)
occurrences (all)	3	4	5
Neutrophil count decreased			
subjects affected / exposed	9 / 63 (14.29%)	2 / 173 (1.16%)	2 / 62 (3.23%)
occurrences (all)	33	2	2
Platelet count decreased			
subjects affected / exposed	6 / 63 (9.52%)	1 / 173 (0.58%)	1 / 62 (1.61%)
occurrences (all)	8	1	1
Weight decreased			
subjects affected / exposed	4 / 63 (6.35%)	14 / 173 (8.09%)	6 / 62 (9.68%)
occurrences (all)	4	14	7
White blood cell count decreased			
subjects affected / exposed	6 / 63 (9.52%)	2 / 173 (1.16%)	1 / 62 (1.61%)
occurrences (all)	21	2	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 63 (7.94%)	9 / 173 (5.20%)	6 / 62 (9.68%)
occurrences (all)	5	10	6
Headache			
subjects affected / exposed	7 / 63 (11.11%)	17 / 173 (9.83%)	9 / 62 (14.52%)
occurrences (all)	8	19	11
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	4 / 63 (6.35%)	2 / 173 (1.16%)	0 / 62 (0.00%)
occurrences (all)	8	3	0
Neutropenia			
subjects affected / exposed	7 / 63 (11.11%)	3 / 173 (1.73%)	0 / 62 (0.00%)
occurrences (all)	40	7	0
Anaemia			
subjects affected / exposed	17 / 63 (26.98%)	17 / 173 (9.83%)	5 / 62 (8.06%)
occurrences (all)	22	18	5
Thrombocytopenia			

subjects affected / exposed	5 / 63 (7.94%)	3 / 173 (1.73%)	1 / 62 (1.61%)
occurrences (all)	10	6	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 63 (12.70%)	31 / 173 (17.92%)	6 / 62 (9.68%)
occurrences (all)	17	39	6
Fatigue			
subjects affected / exposed	10 / 63 (15.87%)	25 / 173 (14.45%)	10 / 62 (16.13%)
occurrences (all)	16	27	10
Pyrexia			
subjects affected / exposed	6 / 63 (9.52%)	20 / 173 (11.56%)	9 / 62 (14.52%)
occurrences (all)	8	27	14
Oedema peripheral			
subjects affected / exposed	3 / 63 (4.76%)	16 / 173 (9.25%)	6 / 62 (9.68%)
occurrences (all)	5	17	8
Non-cardiac chest pain			
subjects affected / exposed	2 / 63 (3.17%)	4 / 173 (2.31%)	4 / 62 (6.45%)
occurrences (all)	3	4	4
Malaise			
subjects affected / exposed	4 / 63 (6.35%)	3 / 173 (1.73%)	1 / 62 (1.61%)
occurrences (all)	8	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 63 (12.70%)	36 / 173 (20.81%)	9 / 62 (14.52%)
occurrences (all)	8	45	13
Nausea			
subjects affected / exposed	15 / 63 (23.81%)	28 / 173 (16.18%)	11 / 62 (17.74%)
occurrences (all)	20	33	12
Stomatitis			
subjects affected / exposed	5 / 63 (7.94%)	10 / 173 (5.78%)	5 / 62 (8.06%)
occurrences (all)	5	11	6
Vomiting			
subjects affected / exposed	4 / 63 (6.35%)	17 / 173 (9.83%)	8 / 62 (12.90%)
occurrences (all)	5	17	8
Abdominal pain			

subjects affected / exposed	4 / 63 (6.35%)	5 / 173 (2.89%)	4 / 62 (6.45%)
occurrences (all)	4	5	4
Constipation			
subjects affected / exposed	15 / 63 (23.81%)	14 / 173 (8.09%)	13 / 62 (20.97%)
occurrences (all)	16	15	15
Abdominal pain upper			
subjects affected / exposed	1 / 63 (1.59%)	2 / 173 (1.16%)	1 / 62 (1.61%)
occurrences (all)	1	2	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 63 (14.29%)	25 / 173 (14.45%)	11 / 62 (17.74%)
occurrences (all)	11	26	12
Rhinorrhoea			
subjects affected / exposed	1 / 63 (1.59%)	4 / 173 (2.31%)	6 / 62 (9.68%)
occurrences (all)	1	4	6
Haemoptysis			
subjects affected / exposed	2 / 63 (3.17%)	6 / 173 (3.47%)	4 / 62 (6.45%)
occurrences (all)	2	7	8
Cough			
subjects affected / exposed	5 / 63 (7.94%)	24 / 173 (13.87%)	11 / 62 (17.74%)
occurrences (all)	5	29	13
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	4 / 63 (6.35%)	4 / 173 (2.31%)	0 / 62 (0.00%)
occurrences (all)	4	4	0
Rash			
subjects affected / exposed	9 / 63 (14.29%)	14 / 173 (8.09%)	3 / 62 (4.84%)
occurrences (all)	9	15	4
Pruritus			
subjects affected / exposed	2 / 63 (3.17%)	28 / 173 (16.18%)	7 / 62 (11.29%)
occurrences (all)	2	36	8
Dermatitis acneiform			
subjects affected / exposed	6 / 63 (9.52%)	6 / 173 (3.47%)	3 / 62 (4.84%)
occurrences (all)	6	11	4
Psychiatric disorders			

Insomnia			
subjects affected / exposed	4 / 63 (6.35%)	6 / 173 (3.47%)	7 / 62 (11.29%)
occurrences (all)	4	6	7
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 63 (0.00%)	14 / 173 (8.09%)	6 / 62 (9.68%)
occurrences (all)	0	15	6
Hyperthyroidism			
subjects affected / exposed	1 / 63 (1.59%)	17 / 173 (9.83%)	2 / 62 (3.23%)
occurrences (all)	1	17	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 63 (3.17%)	9 / 173 (5.20%)	2 / 62 (3.23%)
occurrences (all)	2	11	2
Myalgia			
subjects affected / exposed	3 / 63 (4.76%)	9 / 173 (5.20%)	2 / 62 (3.23%)
occurrences (all)	4	9	2
Musculoskeletal pain			
subjects affected / exposed	4 / 63 (6.35%)	7 / 173 (4.05%)	6 / 62 (9.68%)
occurrences (all)	4	10	8
Musculoskeletal chest pain			
subjects affected / exposed	2 / 63 (3.17%)	7 / 173 (4.05%)	3 / 62 (4.84%)
occurrences (all)	2	7	5
Back pain			
subjects affected / exposed	6 / 63 (9.52%)	11 / 173 (6.36%)	7 / 62 (11.29%)
occurrences (all)	7	13	7
Arthralgia			
subjects affected / exposed	3 / 63 (4.76%)	16 / 173 (9.25%)	7 / 62 (11.29%)
occurrences (all)	3	19	8
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 63 (1.59%)	15 / 173 (8.67%)	3 / 62 (4.84%)
occurrences (all)	1	18	5
Influenza			
subjects affected / exposed	0 / 63 (0.00%)	3 / 173 (1.73%)	2 / 62 (3.23%)
occurrences (all)	0	3	3

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	3 / 63 (4.76%)	3 / 173 (1.73%)	5 / 62 (8.06%)
occurrences (all)	3	3	6
Hyperkalaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 173 (0.00%)	5 / 62 (8.06%)
occurrences (all)	2	0	5
Decreased appetite			
subjects affected / exposed	20 / 63 (31.75%)	34 / 173 (19.65%)	16 / 62 (25.81%)
occurrences (all)	24	39	19
Dehydration			
subjects affected / exposed	1 / 63 (1.59%)	1 / 173 (0.58%)	1 / 62 (1.61%)
occurrences (all)	3	1	1

Non-serious adverse events	Sub-study B: SoC	Sub-study B: Tremelimumab	Sub-study B: Durvalumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 110 (90.91%)	48 / 60 (80.00%)	99 / 117 (84.62%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 110 (2.73%)	2 / 60 (3.33%)	4 / 117 (3.42%)
occurrences (all)	6	2	5
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 110 (7.27%)	5 / 60 (8.33%)	2 / 117 (1.71%)
occurrences (all)	12	6	5
Alanine aminotransferase increased			
subjects affected / exposed	10 / 110 (9.09%)	5 / 60 (8.33%)	5 / 117 (4.27%)
occurrences (all)	15	6	9
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 110 (0.91%)	1 / 60 (1.67%)	1 / 117 (0.85%)
occurrences (all)	1	1	2
Neutrophil count decreased			
subjects affected / exposed	18 / 110 (16.36%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences (all)	43	0	1
Platelet count decreased			
subjects affected / exposed	8 / 110 (7.27%)	0 / 60 (0.00%)	0 / 117 (0.00%)
occurrences (all)	27	0	0

Weight decreased			
subjects affected / exposed	4 / 110 (3.64%)	4 / 60 (6.67%)	8 / 117 (6.84%)
occurrences (all)	4	4	8
White blood cell count decreased			
subjects affected / exposed	11 / 110 (10.00%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences (all)	32	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 110 (4.55%)	3 / 60 (5.00%)	8 / 117 (6.84%)
occurrences (all)	6	3	8
Headache			
subjects affected / exposed	6 / 110 (5.45%)	5 / 60 (8.33%)	8 / 117 (6.84%)
occurrences (all)	8	6	8
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	7 / 110 (6.36%)	1 / 60 (1.67%)	0 / 117 (0.00%)
occurrences (all)	15	1	0
Neutropenia			
subjects affected / exposed	18 / 110 (16.36%)	1 / 60 (1.67%)	0 / 117 (0.00%)
occurrences (all)	48	3	0
Anaemia			
subjects affected / exposed	27 / 110 (24.55%)	5 / 60 (8.33%)	11 / 117 (9.40%)
occurrences (all)	49	5	13
Thrombocytopenia			
subjects affected / exposed	11 / 110 (10.00%)	2 / 60 (3.33%)	4 / 117 (3.42%)
occurrences (all)	15	2	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 110 (15.45%)	9 / 60 (15.00%)	16 / 117 (13.68%)
occurrences (all)	19	9	21
Fatigue			
subjects affected / exposed	24 / 110 (21.82%)	4 / 60 (6.67%)	22 / 117 (18.80%)
occurrences (all)	30	4	24
Pyrexia			
subjects affected / exposed	23 / 110 (20.91%)	6 / 60 (10.00%)	12 / 117 (10.26%)
occurrences (all)	33	7	15

Oedema peripheral			
subjects affected / exposed	9 / 110 (8.18%)	2 / 60 (3.33%)	8 / 117 (6.84%)
occurrences (all)	10	3	10
Non-cardiac chest pain			
subjects affected / exposed	4 / 110 (3.64%)	1 / 60 (1.67%)	2 / 117 (1.71%)
occurrences (all)	4	1	2
Malaise			
subjects affected / exposed	5 / 110 (4.55%)	1 / 60 (1.67%)	8 / 117 (6.84%)
occurrences (all)	5	1	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	18 / 110 (16.36%)	16 / 60 (26.67%)	25 / 117 (21.37%)
occurrences (all)	26	20	33
Nausea			
subjects affected / exposed	22 / 110 (20.00%)	11 / 60 (18.33%)	20 / 117 (17.09%)
occurrences (all)	32	16	25
Stomatitis			
subjects affected / exposed	5 / 110 (4.55%)	1 / 60 (1.67%)	3 / 117 (2.56%)
occurrences (all)	6	3	3
Vomiting			
subjects affected / exposed	8 / 110 (7.27%)	7 / 60 (11.67%)	18 / 117 (15.38%)
occurrences (all)	13	10	22
Abdominal pain			
subjects affected / exposed	2 / 110 (1.82%)	2 / 60 (3.33%)	2 / 117 (1.71%)
occurrences (all)	5	2	2
Constipation			
subjects affected / exposed	11 / 110 (10.00%)	4 / 60 (6.67%)	15 / 117 (12.82%)
occurrences (all)	12	4	16
Abdominal pain upper			
subjects affected / exposed	4 / 110 (3.64%)	2 / 60 (3.33%)	7 / 117 (5.98%)
occurrences (all)	6	2	7
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	15 / 110 (13.64%)	6 / 60 (10.00%)	16 / 117 (13.68%)
occurrences (all)	16	6	17
Rhinorrhoea			

subjects affected / exposed	2 / 110 (1.82%)	1 / 60 (1.67%)	1 / 117 (0.85%)
occurrences (all)	2	1	1
Haemoptysis			
subjects affected / exposed	4 / 110 (3.64%)	1 / 60 (1.67%)	7 / 117 (5.98%)
occurrences (all)	4	1	7
Cough			
subjects affected / exposed	14 / 110 (12.73%)	5 / 60 (8.33%)	15 / 117 (12.82%)
occurrences (all)	15	5	20
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	5 / 110 (4.55%)	3 / 60 (5.00%)	4 / 117 (3.42%)
occurrences (all)	5	3	6
Rash			
subjects affected / exposed	17 / 110 (15.45%)	9 / 60 (15.00%)	7 / 117 (5.98%)
occurrences (all)	17	11	9
Pruritus			
subjects affected / exposed	5 / 110 (4.55%)	14 / 60 (23.33%)	11 / 117 (9.40%)
occurrences (all)	5	17	12
Dermatitis acneiform			
subjects affected / exposed	4 / 110 (3.64%)	0 / 60 (0.00%)	1 / 117 (0.85%)
occurrences (all)	4	0	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 110 (4.55%)	5 / 60 (8.33%)	7 / 117 (5.98%)
occurrences (all)	5	5	7
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 110 (0.91%)	3 / 60 (5.00%)	10 / 117 (8.55%)
occurrences (all)	1	4	11
Hyperthyroidism			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	6 / 117 (5.13%)
occurrences (all)	0	1	7
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	5 / 110 (4.55%)	6 / 60 (10.00%)	9 / 117 (7.69%)
occurrences (all)	5	7	11

Myalgia			
subjects affected / exposed	4 / 110 (3.64%)	1 / 60 (1.67%)	5 / 117 (4.27%)
occurrences (all)	4	1	5
Musculoskeletal pain			
subjects affected / exposed	5 / 110 (4.55%)	1 / 60 (1.67%)	12 / 117 (10.26%)
occurrences (all)	5	1	12
Musculoskeletal chest pain			
subjects affected / exposed	2 / 110 (1.82%)	2 / 60 (3.33%)	7 / 117 (5.98%)
occurrences (all)	2	2	7
Back pain			
subjects affected / exposed	4 / 110 (3.64%)	4 / 60 (6.67%)	14 / 117 (11.97%)
occurrences (all)	4	4	15
Arthralgia			
subjects affected / exposed	2 / 110 (1.82%)	4 / 60 (6.67%)	10 / 117 (8.55%)
occurrences (all)	4	5	10
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 110 (4.55%)	1 / 60 (1.67%)	7 / 117 (5.98%)
occurrences (all)	5	1	8
Influenza			
subjects affected / exposed	0 / 110 (0.00%)	1 / 60 (1.67%)	6 / 117 (5.13%)
occurrences (all)	0	1	6
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 110 (1.82%)	9 / 60 (15.00%)	8 / 117 (6.84%)
occurrences (all)	2	10	10
Hyperkalaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 60 (0.00%)	4 / 117 (3.42%)
occurrences (all)	1	0	5
Decreased appetite			
subjects affected / exposed	23 / 110 (20.91%)	12 / 60 (20.00%)	27 / 117 (23.08%)
occurrences (all)	24	12	28
Dehydration			
subjects affected / exposed	1 / 110 (0.91%)	4 / 60 (6.67%)	0 / 117 (0.00%)
occurrences (all)	1	6	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2014	Key changes from this amendment are listed under Amendment 3.
28 July 2014	Key changes from this amendment are listed under Amendment 3.
08 October 2014	The study design was updated to include 2 independent sub-studies as follows: Sub-study A was designed to enroll PD-L1 high non-small cell lung cancer (NSCLC) participants into either the durvalumab monotherapy arm or SoC treatment arm in a 1:1 ratio. Sub-study B was designed to enroll PD-L1 low/neg NSCLC participants into either durvalumab in combination with tremelimumab treatment arm, durvalumab monotherapy arm, tremelimumab monotherapy arm, or SoC treatment arm in a 1:1:1:1 ratio. PD-L1 tumor status was assessed as part of the pre-screening process. The study objectives were updated to include the additional treatment arms. Participants selection criteria were updated to include new treatment arms, PD-L1 tumor status (including requirements for archival tumor sample), retreatment criteria, additional exclusion criteria for sub-study B, and restrictions during the study. Descriptions of study treatments, treatment regimens, management of toxicity and adverse event of special interest (AESI), treatment compliance, and discontinuation of study treatment were updated. The evaluation and calculation of study variables, and statistical methods were updated.
27 March 2015	Deep sustained response was removed from the secondary objectives and endpoints. The dose regimen for sub-study B durvalumab in combination with tremelimumab treatment arm was updated to durvalumab 20 mg/kg plus tremelimumab 1 mg/kg Q4W IV for up to 12 weeks (4 doses) then durvalumab alone (10 mg/kg Q2W IV, starting at Week 16, for 34 weeks [18 doses]). Randomization to treatment arms for sub-study B was changed to a 3:2:2:1 ratio (durvalumab in combination with tremelimumab: SoC: durvalumab monotherapy: tremelimumab monotherapy, respectively). Language was updated to allow participants enrolled in the durvalumab in combination with tremelimumab treatment arm of sub-study B who progress while in the durvalumab monotherapy period to be retreated with the combination. Clarification of the process of treatment and retreatment in each sub-study was also provided. The exclusion criterion regarding participants with known epidermal growth factor receptor (EGFR) tyrosine kinase (TK) activating mutations was updated to allow participants with EGFR TK inactivating mutations (eg, exon 20) to enroll.
30 December 2015	Language regarding treatment through disease progression and retreatment within the inclusion criteria was updated and moved to a separate section of the protocol. New safety data were added, including an updated list of AESIs and a new appendix containing dose modification and toxicity management guidelines. Inclusion criteria 6 and 7 were updated with new parameters for both mandatory and optional archival tumor samples. Exclusion criterion 2 was updated to exclude participants from other durvalumab studies, and the language regarding participants with tuberculosis in exclusion criterion 25 was updated.

31 August 2016	The number of participants planned, determination of sample size, and statistics were updated. The outcome measures using blinded independent central review (BICR) assessments according to RECIST v1.1 were removed and replaced with Investigator assessments according to RECIST v1.1. The exploratory objective and outcome utilizing BICR assessments according to immune-related response criteria were also removed. Language was updated to clarify that the interim analysis will be conducted for Sub-study B only. The retreatment exclusion criteria were updated to remove the 28-day wash-out period before retreatment. The text regarding immunosuppressive medication was updated, and 3 additional criteria for concomitant medication use were included.
19 September 2017	The maximum period of retreatment was updated for all immunotherapy arms from a maximum of 12 months to as long as the participant gained clinical benefit, as judged by the Investigator. The dose modification and toxicity management guidelines for immune-mediated, infusion-related, and non immune-mediated reactions were updated, and language was updated on AESIs, including the list of AESIs. Language was added regarding timing of final PFS and OS analyses.
08 January 2018	The toxicity management guidelines for immune-mediated, infusion-related, and non-immune-mediated reactions and list of AESIs were updated.
07 February 2020	Toxicity management guidelines will be a separate annex to the protocol. Administrative changes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported