Clinical trial results:
A Phase 1b Open-label Study to Evaluate the Safety and Tolerability of MEDI4736 in Combination with Tremelimumab in Subjects with Advanced Non-small Cell Lung Cancer

Summary

EudraCT number	2015-003715-38
Trial protocol	BE ES DE GB FR
Global end of trial date	17 September 2019

Results information

Result version number	v1 (current)
This version publication date	26 September 2020
First version publication date	26 September 2020

Trial information

Trial identification

Sponsor protocol code	D4190C00006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02000947
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, CB21 6GH
Public contact	Shahram Rahimian, MedImmune, LLC, +1 800-236-9933, information.center@astrazeneca.com
Scientific contact	Shahram Rahimian, MedImmune, LLC, +1 800-236-9933, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2019
Global end of trial reached?	Yes
Global end of trial date	17 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives in dose-escalation phase are: 1) to determine maximum tolerated dose (MTD) or highest protocol-defined dose in absence of exceeding MTD and safety profile of MEDI4736 and tremelimumab in participants with advanced non-small cell lung cancer (NSCLC) using every 2 weeks (Q2W) and every 4 weeks (Q4W) schedules. Primary objectives in dose-expansion phase are: 1) To determine safety profile of MEDI4736 and tremelimumab at the recommended dose Q4W in treatment-naïve and immunotherapy-naive participants, and participants with refractory and relapsed disease 2) To determine antitumor activity of MEDI4736 and tremelimumab at the recommended dose Q4W in immunotherapy-naive participants and participants with refractory and relapsed disease 3) To evaluate safety profile of MEDI4736 monotherapy in participants who have experienced immune-mediated treatment-emergent adverse events (imTEAEs) after discontinuing MEDI4736 in combination with tremelimumab

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 318
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Korea, Republic of: 60
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United Kingdom: 10
Worldwide total number of subjects	457
EEA total number of subjects	76

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)	220
From 65 to 84 years	235
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 25Oct2013 to 17Sep2019.

Pre-assignment

Screening details:

A total of 102 participants were enrolled and treated in dose-escalation arms and a total of 355 participants were enrolled and treated in dose-expansion arms.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Total Escalation

Arm description:

Participants received MEDI4736 IV escalation doses (Dose 1 or 2 or 3 or 4) every 4 weeks (Q4W; up to 13 doses) or every two weeks (Q2W; up to 26 doses) and IV tremelimumab dose (Dose 1, 2, or 3) Q4W for 6 doses and then every 12 weeks (Q12W) for 3 doses (up to 9 doses in total) for 12 months or until disease progression.

Arm type	Experimental
Investigational medicinal product name	MEDI4736
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MEDI4736 escalation doses (Dose 1 or 2 or 3 or 4) were administered intravenously Q4W (up to 13 doses) or Q2W (up to 26 doses) for 12 months.

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 dose (Dose 1 or 2 or 3) was administered intravenously Q4W for 6 doses and then Q12W for 3 doses (up to 9 doses in total) for 12 months.

Arm title	Expansion Cohort A

Arm description:

Treatment-naïve, non-epidermal growth factor receptor (non-EGFR) mutation positive, and non-anaplastic lymphoma kinase (non-ALK) rearrangement positive participants received IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.

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 Dose 1 Q4W was administered intravenously for 4 doses.

Investigational medicinal product name	MEDI4736
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MEDI4736 Dose 4 Q4W was administered intravenously to complete a total of 12 months of therapy.

Arm title	Expansion Cohort B (Coadmin)

Arm description:

Immunotherapy-naive participants received co-administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.

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 Dose 1 Q4W was administered intravenously for 4 doses.

Investigational medicinal product name	MEDI4736
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MEDI4736 Dose 4 Q4W was administered intravenously to complete a total of 12 months of therapy.

Arm title	Expansion Cohort B (Sequential)

Arm description:

Immunotherapy-naive participants received sequential administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W monotherapy for 9 doses to complete a total of 12 months of therapy or until disease progression.

Arm type	Experimental
Investigational medicinal product name	MEDI4736
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intratumoral use, Intravenous use

Dosage and administration details:

MEDI4736 Dose 4 Q4W was administered intravenously to complete a total of 12 months of therapy.

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 Dose 1 Q4W was administered intravenously for 4 doses.

Arm title	Expansion Cohort C (Refractory)

Arm description:

Participants who were refractory to previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.

Arm type	Experimental
Investigational medicinal product name	MEDI4736
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

MEDI4736 Dose 4 Q4W was administered intravenously to complete a total of 12 months of therapy.

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 Dose 1 Q4W was administered intravenously for 4 doses.

Arm title	Expansion Cohort C (Relapsed)

Arm description:

Participants whom disease was relapsed with the previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy.

Arm type	Experimental
Investigational medicinal product name	MEDI4736
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MEDI4736 Dose 4 Q4W was administered intravenously to complete a total of 12 months of therapy.

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 Dose 1 Q4W was administered intravenously for 4 doses.

Number of subjects in period 1	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)
Started	102	45	19
Completed	0	1	0
Not completed	102	44	19
Adverse event, serious fatal	66	24	15
Consent withdrawn by subject	21	15	3
Unspecified	12	4	1
Lost to follow-up	3	1	-

Number of subjects in period 1	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)
Started	213	38	40
Completed	3	0	0
Not completed	210	38	40
Adverse event, serious fatal	126	28	31
Consent withdrawn by subject	26	6	6
Unspecified	52	3	2
Lost to follow-up	6	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Total Escalation
Reporting group description:	
Participants received MEDI4736 IV escalation doses (Dose 1 or 2 or 3 or 4) every 4 weeks (Q4W; up to 13 doses) or every two weeks (Q2W; up to 26 doses) and IV tremelimumab dose (Dose 1, 2, or 3) Q4W for 6 doses and then every 12 weeks (Q12W) for 3 doses (up to 9 doses in total) for 12 months or until disease progression.	
Reporting group title	Expansion Cohort A
Reporting group description:	
Treatment-naïve, non-epidermal growth factor receptor (non-EGFR) mutation positive, and non-anaplastic lymphoma kinase (non-ALK) rearrangement positive participants received IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort B (Coadmin)
Reporting group description:	
Immunotherapy-naive participants received co-administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort B (Sequential)
Reporting group description:	
Immunotherapy-naive participants received sequential administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W monotherapy for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort C (Refractory)
Reporting group description:	
Participants who were refractory to previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort C (Relapsed)
Reporting group description:	
Participants whom disease was relapsed with the previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy.	

Reporting group values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)
Number of subjects	102	45	19
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	11	9
From 65-84 years	67	33	10
85 years and over	1	1	0

Age Continuous			
Units: Years			
arithmetic mean	65.3	68.4	62.8
standard deviation	± 9.6	± 8.3	± 10.5
Sex: Female, Male			
Units:			
Female	47	21	12
Male	55	24	7
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	5	2	0
Black or African American	1	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
White	95	42	17
Other	1	0	1
Not reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	2	1
Not Hispanic or Latino	99	43	17
Unknown or Not Reported	0	0	1

Reporting group values	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)
Number of subjects	213	38	40
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	126	15	25
From 65-84 years	87	23	15
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	61.2	66.5	62.3
standard deviation	± 10.4	± 8.2	± 8.0
Sex: Female, Male			
Units:			
Female	80	12	17
Male	133	26	23
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	64	2	3
Black or African American	2	1	2

Native Hawaiian or Other Pacific Islander	1	0	1
White	133	34	30
Other	6	1	1
Not reported	7	0	3
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	12	1	1
Not Hispanic or Latino	194	36	37
Unknown or Not Reported	7	1	2

Reporting group values	Total		
Number of subjects	457		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	220		
From 65-84 years	235		
85 years and over	2		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units:			
Female	189		
Male	268		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaskan Native	0		
Asian	76		
Black or African American	8		
Native Hawaiian or Other Pacific Islander	2		
White	351		
Other	10		
Not reported	10		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	20		
Not Hispanic or Latino	426		
Unknown or Not Reported	11		

End points

End points reporting groups

Reporting group title	Total Escalation
Reporting group description:	
Participants received MEDI4736 IV escalation doses (Dose 1 or 2 or 3 or 4) every 4 weeks (Q4W; up to 13 doses) or every two weeks (Q2W; up to 26 doses) and IV tremelimumab dose (Dose 1, 2, or 3) Q4W for 6 doses and then every 12 weeks (Q12W) for 3 doses (up to 9 doses in total) for 12 months or until disease progression.	
Reporting group title	Expansion Cohort A
Reporting group description:	
Treatment-naïve, non-epidermal growth factor receptor (non-EGFR) mutation positive, and non-anaplastic lymphoma kinase (non-ALK) rearrangement positive participants received IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort B (Coadmin)
Reporting group description:	
Immunotherapy-naive participants received co-administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort B (Sequential)
Reporting group description:	
Immunotherapy-naive participants received sequential administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W monotherapy for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort C (Refractory)
Reporting group description:	
Participants who were refractory to previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.	
Reporting group title	Expansion Cohort C (Relapsed)
Reporting group description:	
Participants whom disease was relapsed with the previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy.	
Subject analysis set title	Escalation MEDI4736 Dose 1 (Q4W)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received IV MEDI4736 Dose 1 Q4W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.	
Subject analysis set title	Escalation MEDI4736 Dose 2 (Q4W)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received IV MEDI4736 Dose 2 Q4W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.	
Subject analysis set title	Escalation MEDI4736 Dose 3 (Q4W)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received IV MEDI4736 Dose 3 Q4W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.	
Subject analysis set title	Escalation & Expansion MEDI4736 Dose 4 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In escalation part of the study, participants received IV MEDI4736 Dose 4 Q4W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months. in expansion part of the study, participants received IV MEDI4736 Dose 4 Q4W and IV tremelimumab Q4W for up to 4 doses each, followed by IV MEDI4736 Dose 4 Q4W monotherapy for 9 doses for a total duration of 12 months.

Subject analysis set title	Escalation MEDI4736 Dose 2 (Q2W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Dose 2 Q2W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Escalation MEDI4736 Dose 2 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Dose 2 Q4W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Escalation MEDI4736 Dose 3 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Dose 3 Q4W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Escalation Tremelimumab Dose 1 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Q4W/Q2W for 12 months and IV tremelimumab Dose 1 Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Escalation Tremelimumab Dose 2 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Q4W/Q2W for 12 months and IV tremelimumab Dose 2 Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Escalation Tremelimumab Dose 3 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Q4W and IV tremelimumab Dose 3 Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Expansion Tremelimumab Dose 1 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Q4W and IV tremelimumab Dose 1 Q4W for 4 doses, followed IV MEDI4736 Q4W monotherapy for 12 months in expansion part of the study.

Subject analysis set title	Escalation & Expansion MEDI4736 Dose 4 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In escalation part of the study, participants received IV MEDI4736 Dose 4 Q4W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months. in expansion part of the study, participants received IV MEDI4736 Dose 4 Q4W and IV tremelimumab Q4W for up to 4 doses each, followed IV MEDI4736 Dose 4 Q4W monotherapy for 9 doses for a total duration of 12 months.

Subject analysis set title	Escalation MEDI4736 Dose 2 (Q2W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Dose 2 Q2W for 12 months and IV tremelimumab Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Escalation Tremelimumab Dose 1 (Q4W)

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Q4W/Q2W for 12 months and IV tremelimumab Dose 1 Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Escalation Tremelimumab Dose 2 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Q4W/Q2W for 12 months and IV tremelimumab Dose 2 Q4W for 6 doses and then Q12W for 3 doses (for a total of up to 9 doses) for 12 months in escalation part of the study.

Subject analysis set title	Expansion Tremelimumab Dose 1 (Q4W)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received IV MEDI4736 Q4W and IV tremelimumab Dose 1 Q4W for 4 doses, followed IV MEDI4736 Q4W monotherapy for 12 months in expansion part of the study.

Primary: Number of Participants With Dose-limiting Toxicities (DLT) in the Dose-escalation phase

End point title	Number of Participants With Dose-limiting Toxicities (DLT) in the Dose-escalation phase[1][2]

End point description:

A DLT was defined as any Grade 3 or higher treatment-related toxicity that occurred during DLT-evaluation period including any >=Grade 3 colitis, Grade 4 immune-related adverse event (irAE; AEs of immune nature in absence of a clear alternative etiology), Grade 3 irAE that does not downgrade to <=Grade 2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to <=Grade 1 or baseline within 14 days, liver transaminase elevation higher than 8×upper limit of normal (ULN) or total bilirubin higher than 5×ULN, any >=Grade 2 pneumonitis that does not resolve to <=Grade 1 within 3 days of the initiation of maximal supportive care. DLT evaluable population included all participants enrolled in the dose-escalation phase who received the protocol-assigned treatment with MEDI4736 and tremelimumab, and completed the safety follow-up through the DLT evaluation period or experienced a DLT or died during the DLT evaluation period.

End point type	Primary

End point timeframe:

From the first dose of MEDI4736 (Day 1) until third dose of MEDI4736 Dose 1 (Day 57) and until second dose of MEDI4736 for other MEDI4736 doses (Day 29)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[2] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Total Escalation			
Subject group type	Reporting group			
Number of subjects analysed	100			
Units: Participants	2			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)[3][4]

End point description:

An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Primary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[4] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort C (Refractory)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	45	19	38
Units: Participants				
Any TEAE	101	44	19	37
Any TESAE	68	20	11	26

End point values	Expansion Cohort C (Relapsed)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Participants				
Any TEAE	38			
Any TESAE	22			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs

End point title	Number of Participants With Abnormal Clinical Laboratory

	Parameters Reported as TEAEs[5][6]

End point description:

Number of participants with clinical laboratory abnormalities reported as TEAEs are reported. Clinical laboratory abnormalities are defined as any abnormal findings in analysis of serum chemistry, hematology, coagulation, and urine. The data for TEAEs >=5% frequency in any arm are reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Primary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[6] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort C (Refractory)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	45	19	38
Units: Participants				
Anemia	20	5	2	2
international normalized ratio increased	1	1	2	0
Activated partial thromboplastin time prolonged	0	0	2	1
Blood fibrinogen increased	0	0	1	0
Alanine aminotransferase increased	13	4	3	0
Aspartate aminotransferase increased	11	2	4	0
Gamma glutamyl transferase increased	11	1	1	2
Blood alkaline phosphatase increased	5	3	3	1
Hypoalbuminemia	0	3	2	0
Hyperbilirubinemia	0	0	1	1
Transaminases increased	0	1	1	0
Acute kidney injury	4	3	1	0
Blood creatinine increased	11	1	1	2
Proteinuria	5	1	1	0
Hematuria	0	1	1	0
Pollakiuria	0	3	1	0
Chromaturia	0	1	1	0
Polyuria	0	0	1	0
Amylase increased	20	8	1	2
Lipase increased	15	6	3	1
Hyperglycemia	11	3	2	2
Hypomagnesemia	8	2	0	5
Hyponatremia	7	5	3	5
Hypokalemia	5	5	1	3
Hypercalcemia	2	3	0	1
Hyperkalemia	2	2	1	1
Hypertriglyceridemia	2	0	2	1
Hypocalcemia	1	2	1	0

Hypoglycemia	0	0	1	1
Blood cholesterol increased	0	0	1	0
Lymphocyte count decreased	1	1	0	0
Blood triglycerides increased	1	0	0	0

End point values	Expansion Cohort C (Relapsed)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Participants				
Anemia	7			
international normalized ratio increased	0			
Activated partial thromboplastin time prolonged	0			
Blood fibrinogen increased	0			
Alanine aminotransferase increased	3			
Aspartate aminotransferase increased	2			
Gamma glutamyl transferase increased	1			
Blood alkaline phosphatase increased	3			
Hypoalbuminemia	3			
Hyperbilirubinemia	1			
Transaminases increased	0			
Acute kidney injury	1			
Blood creatinine increased	3			
Proteinuria	1			
Hematuria	0			
Pollakiuria	0			
Chromaturia	0			
Polyuria	0			
Amylase increased	1			
Lipase increased	4			
Hyperglycemia	4			
Hypomagnesemia	2			
Hyponatremia	4			
Hypokalemia	7			
Hypercalcemia	0			
Hyperkalemia	2			
Hypertriglyceridemia	2			
Hypocalcemia	1			
Hypoglycemia	0			
Blood cholesterol increased	0			
Lymphocyte count decreased	2			
Blood triglycerides increased	3			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Vital Signs and Physical Examinations Reported as TEAEs

End point title	Number of Participants With Abnormal Vital Signs and Physical Examinations Reported as TEAEs[7][8]

End point description:

Number of participants with abnormal vital signs and physical examinations reported as TEAEs are reported. Abnormal vital signs and physical examinations reported as TEAEs included any abnormal findings in body temperature, blood pressure, pulse rate, respiratory rate, and body weight. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Primary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[8] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort C (Refractory)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	45	19	38
Units: Participants				
Pyrexia	21	4	2	4
Hypotension	7	1	3	1
Hypoxia	7	2	3	2
Hypertension	6	1	0	2
Weight decreased	6	4	3	5
Heart rate irregular	1	0	0	0
Palpitations	1	1	1	0
Respiratory distress	0	0	1	0

End point values	Expansion Cohort C (Relapsed)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Participants				
Pyrexia	2			
Hypotension	3			
Hypoxia	3			
Hypertension	1			
Weight decreased	5			
Heart rate irregular	0			
Palpitations	0			

Respiratory distress	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Abnormal Electrocardiogram (ECG) Reported as TEAEs

End point title	Number of Participants With Abnormal Electrocardiogram (ECG) Reported as TEAEs[9][10]

End point description:

Number of participants with abnormal ECG reported as TEAEs are reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Primary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[10] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort C (Refractory)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	45	19	38
Units: Participants				
Sinus tachycardia	5	1	0	1
Atrial fibrillation	4	3	4	0
Sinus bradycardia	2	0	0	0
Tachycardia	2	0	0	1
Bradycardia	1	0	0	0
Electrocardiogram QT prolonged	0	1	0	0

End point values	Expansion Cohort C (Relapsed)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Participants				
Sinus tachycardia	2			
Atrial fibrillation	0			

Sinus bradycardia	0			
Tachycardia	1			
Bradycardia	0			
Electrocardiogram QT prolonged	0			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Objective Response (OR) per Blinded Independent Central Review (BICR) in Expansion Cohort B (Sequential Administration) and Cohort C

End point title	Percentage of Participants With Objective Response (OR) per Blinded Independent Central Review (BICR) in Expansion Cohort B (Sequential Administration) and Cohort C[11][12]

End point description:

The OR is defined as best overall response of confirmed complete response (CR) or confirmed partial response (PR) based on Response Evaluation Criteria in Solid Tumours (RECIST v1.1). The CR is defined as disappearance of all target and non-target lesions and no new lesions. A confirmed CR is defined as two CRs that were separated by at least 28 days with no evidence of progression in-between. The PR is defined as >= 30% decrease in the sum of diameters of target lesions (compared to baseline) and no new non-target lesion. A confirmed PR is defined as two PRs or an un-confirmed PR and an un-confirmed CR that were separated by at least 28 days with no evidence of progression in-between. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Primary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[12] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	213	38	40	
Units: Percentage of participants				
number (confidence interval 95%)	16.9 (12.1 to 22.6)	5.3 (0.6 to 17.7)	0 (0 to 8.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Immune-mediated Treatment-emergent

Adverse Events (imTEAEs) and Immune-mediated Treatment-emergent Serious Adverse Events (imTESAEs) for Dose-expansion Cohorts

End point title	Number of Participants With Immune-mediated Treatment-emergent Adverse Events (imTEAEs) and Immune-mediated Treatment-emergent Serious Adverse Events (imTESAEs) for Dose-expansion Cohorts[13][14]

End point description:

Immune-mediated AEs are defined as any adverse events of special interest (AESI, excluding AESIs of infusion related/ hypersensitivity/ anaphylactic reactions) that required the use of systemic steroids, endocrine therapy, or other immunosuppressants; were consistent with an immune mediated mechanism of action; and no clear alternate etiology. An AESI is one of scientific and medical interest specific event for understanding of the study drugs and may require close monitoring and rapid communication by the investigator to the sponsor. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Primary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[14] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	19	213	38
Units: Participants				
Any imTEAE	13	6	73	9
Any imTESAE	4	3	22	4

End point values	Expansion Cohort C (Relapsed)			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Participants				
Any imTEAE	14			
Any imTESAE	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With OR per Investigator Assessment

End point title	Percentage of Participants With OR per Investigator

	Assessment

End point description:

The OR is defined as best overall response of confirmed CR or confirmed PR based on RECIST v1.1. The CR is defined as disappearance of all target and non-target lesions and no new lesions. A confirmed CR is defined as two CRs that were separated by at least 28 days with no evidence of progression in-between. The PR is defined as >= 30% decrease in the sum of diameters of target lesions (compared to baseline) and no new non-target lesion. A confirmed PR is defined as two PRs or an un-confirmed PR and an un-confirmed CR that were separated by at least 28 days with no evidence of progression in-between. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort B (Sequential)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	45	19	213
Units: Percentage of participants				
number (confidence interval 95%)	16.7 (10.0 to 25.3)	15.6 (6.5 to 29.5)	0 (0 to 17.6)	19.7 (14.6 to 25.7)

End point values	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	40		
Units: Percentage of participants				
number (confidence interval 95%)	7.9 (1.7 to 21.4)	5.0 (0.6 to 16.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) per Investigator Assessment

End point title	Duration of Response (DoR) per Investigator Assessment

End point description:

The DoR is defined as duration from first documentation of OR (confirmed CR or PR) to first documented disease progression based on RECIST V 1.1 or death due to any cause, whichever occurred first. A confirmed CR is defined as 2 CRs (disappearance of all target and non-target lesions and no new lesions) and a confirmed PR is defined as 2 PRs (>= 30% decrease in the sum of diameters of target lesions compared to baseline and no new non-target lesion) or an un-confirmed PR and an un-confirmed CR, both CR and/or PR were separated by at least 28 days with no evidence of progression in-between. The DoR was estimated using Kaplan-Meier method. The arbitrary number "9999" signifies that upper limit of confidence interval was not calculated due to an insufficient number of participants achieved OR for the specified arm. As-treated population with participants who achieved OR per investigator assessment was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort B (Sequential)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	7	0[15]	42
Units: Weeks				
median (confidence interval 95%)	126.1 (20.1 to 9999)	24.4 (14.9 to 9999)	(to)	54.1 (40.3 to 9999)

Notes:

[15] - No participant achieved OR, so no participant was analysed.

End point values	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Weeks				
median (confidence interval 95%)	23.0 (17.0 to 9999)	45.8 (24.1 to 67.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: DoR per BICR

End point title	DoR per BICR[16]

End point description:

The DoR is defined as duration from first documentation of OR (confirmed CR or PR) to first documented disease progression based on RECIST V 1.1 or death due to any cause, whichever occurred first. A confirmed CR is defined as 2 CRs (disappearance of all target and non-target lesions and no new lesions) and a confirmed PR is defined as 2 PRs (>= 30% decrease in the sum of diameters of target lesions compared to baseline and no new non-target lesion) or an un-confirmed PR and an un-confirmed CR, both CR and/or PR were separated by at least 28 days with no evidence of progression in-between. The DoR was estimated using Kaplan-Meier method. The arbitrary number "9999" signifies that upper limit of confidence interval was not calculated due to an insufficient number of participants achieved OR for the specified arm. As-treated population with participants who achieved OR per BICR was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	2	0[17]	
Units: Weeks				
median (confidence interval 95%)	123.0 (53.9 to 9999)	9999 (9999 to 9999)	(to)	

Notes:

[17] - No participant achieved OR, so no participant was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Disease Control (DC) per Investigator Assessment

End point title	Percentage of Participants with Disease Control (DC) per Investigator Assessment

End point description:

Disease control is defined as a best overall response of confirmed CR, confirmed PR, or stable disease (SD) based on RECIST V 1.1. A confirmed CR is defined as two CRs (disappearance of all target and non-target lesions and no new lesions) that were separated by at least 28 days with no evidence of progression in-between. A confirmed PR is defined as two PRs (>= 30% decrease in the sum of diameters of target lesions compared to baseline and no new non-target lesion) or an un-confirmed PR and an un-confirmed CR that were separated by at least 28 days with no evidence of progression in-between. The SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression. The DC per investigator assessment is reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort B (Sequential)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	45	19	213
Units: Percentage of participants				
number (confidence interval 95%)	47.1 (37.1 to 57.2)	57.8 (42.2 to 72.3)	47.4 (24.4 to 71.1)	54.9 (48.0 to 61.7)

End point values	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	40		
Units: Percentage of participants				
number (confidence interval 95%)	28.9 (15.4 to 45.9)	45.0 (29.3 to 61.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with DC per BICR

End point title	Percentage of participants with DC per BICR[18]

End point description:

Disease control is defined as a best overall response of confirmed CR, confirmed PR, or SD based on RECIST V 1.1. A confirmed CR is defined as two CRs (disappearance of all target and non-target lesions and no new lesions) that were separated by at least 28 days with no evidence of progression in-between. A confirmed PR is defined as two PRs (>= 30% decrease in the sum of diameters of target lesions compared to baseline and no new non-target lesion) or an un-confirmed PR and an un-confirmed CR that were separated by at least 28 days with no evidence of progression in-between. The SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progression. The DC per BICR is reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[18] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	213	38	40	
Units: Percentage of participants				
number (confidence interval 95%)	51.2 (44.3 to 58.1)	28.9 (15.4 to 45.9)	40.0 (24.9 to 56.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) per Investigator Assessment

End point title	Progression-free Survival (PFS) per Investigator Assessment

End point description:

The PFS is defined as the time from the start of study drug until the first documentation of disease progression based on RECIST V 1.1 or death due to any cause, whichever occurred first, regardless of whether the participant withdrew from study treatment or received another anticancer therapy prior to progression. PFS per investigator assessment is reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for this outcome

measure.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort B (Sequential)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	33	16	181
Units: Months				
median (confidence interval 95%)	2.6 (1.7 to 4.8)	3.5 (1.7 to 7.2)	2.8 (1.6 to 4.7)	3.5 (1.8 to 4.0)

End point values	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	36		
Units: Months				
median (confidence interval 95%)	1.7 (1.6 to 1.8)	2.2 (1.6 to 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per BICR

End point title	PFS per BICR[19]

End point description:

The PFS is defined as the time from the start of study drug until the first documentation of disease progression based on RECIST V 1.1 or death due to any cause, whichever occurred first, regardless of whether the participant withdrew from study treatment or received another anticancer therapy prior to progression. PFS per BICR is reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for this outcome measure.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[19] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	166	31	34	
Units: Months				
median (confidence interval 95%)	3.5 (1.7 to 3.6)	1.7 (1.6 to 2.6)	2.0 (1.6 to 3.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The OS is defined as the time from the start of study treatment until death due to any cause. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for this outcome measure.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

End point values	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)	Expansion Cohort B (Sequential)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	24	15	126
Units: Months				
median (confidence interval 95%)	14.6 (8.7 to 23.0)	22.1 (14.0 to 29.8)	7.6 (4.4 to 17.9)	14.3 (10.0 to 18.9)

End point values	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	31		
Units: Months				
median (confidence interval 95%)	8.3 (6.0 to 10.4)	8.5 (4.0 to 14.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With TEAEs and TESAEs for Cohort B (Sequential Administration)

End point title	Number of Participants With TEAEs and TESAEs for Cohort B (Sequential Administration)[20]

End point description:

An AE is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[20] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: Participants				
Any TEAE	211			
Any TESAE	120			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs for Cohort B (Sequential Administration)

End point title	Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs for Cohort B (Sequential Administration)[21]

End point description:

Number of participants with clinical laboratory abnormalities reported as TEAEs are reported. Clinical laboratory abnormalities are defined as any abnormal findings in analysis of serum chemistry, hematology, coagulation, and urine. The data for TEAEs >=5% frequency in any arm are reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[21] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: Participants				
Anemia	41			
Alanine aminotransferase increased	15			
Aspartate aminotransferase increased	17			
Amylase increased	28			
Lipase increased	16			
Hyperglycemia	11			
Hyponatremia	12			
Hypokalemia	11			
Hypercalcemia	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Vital Signs and Physical Examinations Reported as TEAES for Cohort B (Sequential Administration)

End point title	Number of Participants With Abnormal Vital Signs and Physical Examinations Reported as TEAES for Cohort B (Sequential Administration)[22]

End point description:

Number of participants with abnormal vital signs and physical examinations reported as TEAEs are reported. Abnormal vital signs and physical examinations reported as TEAEs included any abnormal findings in body temperature, blood pressure, pulse rate, respiratory rate, and body weight. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[22] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: Participants				
Pyrexia	33			
Hypotension	11			
Hypoxia	5			
Hypertension	5			
Weight decreased	19			
Palpitations	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal ECG Reported as TEAES for Cohort B (Sequential Administration)

End point title	Number of Participants With Abnormal ECG Reported as TEAES for Cohort B (Sequential Administration)[23]

End point description:

Number of participants with abnormal ECG reported as TEAEs are reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) was considered for this endpoint.

End point type	Secondary

End point timeframe:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Notes:

[23] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)			
Subject group type	Reporting group			
Number of subjects analysed	213			
Units: Participants				
Sinus tachycardia	3			
Atrial fibrillation	1			
Sinus bradycardia	1			
Tachycardia	7			
Bradycardia	1			
Electrocardiogram T wave inversion	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of MEDI4736 After First Dose

End point title	Maximum Observed Concentration (Cmax) of MEDI4736 After First Dose

End point description:

The Cmax of MEDI4736 is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of MEDI4736 and had any post-dose PK data point was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for the

specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q2W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion) and Day 29 (predose)

End point values	Escalation MEDI4736 Dose 1 (Q4W)	Escalation MEDI4736 Dose 2 (Q4W)	Escalation MEDI4736 Dose 3 (Q4W)	Escalation & Expansion MEDI4736 Dose 4 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	35	231
Units: µg/mL				
geometric mean (geometric coefficient of variation)	67.3 (± 14.9)	259 (± 19.6)	296 (± 33.7)	409 (± 45.7)

End point values	Escalation MEDI4736 Dose 2 (Q2W)			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	224 (± 23.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve From Day 1 to Day 28 (AUC0-28) of MEDI4736 After First Dose

End point title	Area Under the Concentration-time Curve From Day 1 to Day 28 (AUC0-28) of MEDI4736 After First Dose

End point description:

The AUC0-28 of MEDI4736 is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of MEDI4736 and had any post-dose PK data point was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for the specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q2W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion) and Day 29 (predose)

End point values	Escalation MEDI4736 Dose 1 (Q4W)	Escalation MEDI4736 Dose 2 (Q4W)	Escalation MEDI4736 Dose 3 (Q4W)	Escalation & Expansion MEDI4736 Dose 4 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	28	24
Units: µg*day/mL				
geometric mean (geometric coefficient of variation)	639 (± 7.45)	2728 (± 5.06)	3068 (± 21.9)	4209 (± 33.2)

End point values	Escalation MEDI4736 Dose 2 (Q2W)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[24]			
Units: µg*day/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[24] - No participant was analysed for this endpoint for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Concentration (Tmax) of MEDI4736 After First Dose

End point title	Time to Reach Maximum Observed Concentration (Tmax) of MEDI4736 After First Dose

End point description:

The Tmax of MEDI4736 is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of MEDI4736 and had any post-dose PK data point was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for the specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q2W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion) and Day 29 (predose)

End point values	Escalation MEDI4736 Dose 1 (Q4W)	Escalation MEDI4736 Dose 2 (Q4W)	Escalation MEDI4736 Dose 3 (Q4W)	Escalation & Expansion MEDI4736 Dose 4 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	3	35	231
Units: Days				
geometric mean (geometric coefficient of variation)	0.172 (± 1.7)	0.047 (± 4.3)	0.048 (± 11.1)	0.049 (± 24.5)

End point values	Escalation MEDI4736 Dose 2 (Q2W)			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: Days				
geometric mean (geometric coefficient of variation)	0.046 (± 8.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough serum concentration (Ctrough) of MEDI4736 After First Dose

End point title	Trough serum concentration (Ctrough) of MEDI4736 After First Dose

End point description:

The Ctrough of MEDI4736 is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of MEDI4736 and had any post-dose PK data point was considered for this endpoint. The "Number of Participants Analysed" denotes the number of participants evaluated for the specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q2W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post MEDI4736 infusion) and Day 29 (predose)

End point values	Escalation MEDI4736 Dose 1 (Q4W)	Escalation MEDI4736 Dose 2 (Q4W)	Escalation MEDI4736 Dose 3 (Q4W)	Escalation & Expansion MEDI4736 Dose 4 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	2	5	29	37
Units: µg/mL				
geometric mean (geometric coefficient of variation)	8.72 (± 29.5)	36.5 (± 21.8)	43.0 (± 124)	55.5 (± 47.7)

End point values	Escalation MEDI4736 Dose 2 (Q2W)			
Subject group type	Subject analysis set			
Number of subjects analysed	0[25]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[25] - No participant was analysed for this endpoint for this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Tremelimumab After First Dose

End point title	Cmax of Tremelimumab After First Dose

End point description:

The Cmax of tremelimumab is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of tremelimumab and had any post-dose PK data point was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for the specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q4W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion) and Day 29 (predose)

End point values	Escalation Tremelimumab Dose 1 (Q4W)	Escalation Tremelimumab Dose 2 (Q4W)	Escalation Tremelimumab Dose 3 (Q4W)	Expansion Tremelimumab Dose 1 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	32	9	200
Units: µg/mL				
geometric mean (geometric coefficient of variation)	22.5 (± 36.8)	57.5 (± 57.2)	192 (± 15.1)	20.3 (± 37.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Tremelimumab After First Dose

End point title	Tmax of Tremelimumab After First Dose

End point description:

The Tmax of tremelimumab is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of tremelimumab and had any post-dose PK data point was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for the specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q4W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion) and Day 29 (predose)

End point values	Escalation Tremelimumab Dose 1 (Q4W)	Escalation Tremelimumab Dose 2 (Q4W)	Escalation Tremelimumab Dose 3 (Q4W)	Expansion Tremelimumab Dose 1 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	32	9	200
Units: Days				
geometric mean (geometric coefficient of variation)	0.047 (± 12.7)	0.046 (± 8.81)	0.047 (± 11.3)	0.046 (± 13.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough of Tremelimumab After First Dose

End point title	Ctrough of Tremelimumab After First Dose

End point description:

The Ctrough of tremelimumab is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of tremelimumab and had any post-dose PK data point was considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for the specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q4W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion) and Day 29 (predose)

End point values	Escalation Tremelimumab Dose 1 (Q4W)	Escalation Tremelimumab Dose 2 (Q4W)	Escalation Tremelimumab Dose 3 (Q4W)	Expansion Tremelimumab Dose 1 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	22	6	19
Units: µg/mL				
geometric mean (geometric coefficient of variation)	2.65 (± 75.1)	9.51 (± 33.6)	19.5 (± 122)	3.26 (± 59.6)

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-28 days of Tremelimumab After First Dose

End point title	AUC0-28 days of Tremelimumab After First Dose

End point description:

The AUC0-28 days of tremelimumab is reported. Pharmacokinetic evaluable population included all participants who received at least 1 dose of tremelimumab and had any post-dose PK data point was

considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants evaluated for the specified arm.

End point type	Secondary

End point timeframe:

Escalation part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion), Days 8 and 15, and Day 29 (predose); Escalation part (Q4W) and Expansion part (Q4W): Day 1 (predose and 10 minutes post tremelimumab infusion) and Day 29 (predose)

End point values	Escalation Tremelimumab Dose 1 (Q4W)	Escalation Tremelimumab Dose 2 (Q4W)	Escalation Tremelimumab Dose 3 (Q4W)	Expansion Tremelimumab Dose 1 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	36	17	9	14
Units: µg*day/mL				
geometric mean (geometric coefficient of variation)	203 (± 46.5)	625 (± 24.1)	1800 (± 25.1)	239 (± 33.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive Anti-drug Antibodies (ADA) to MEDI4736

End point title	Number of Participants With Positive Anti-drug Antibodies (ADA) to MEDI4736

End point description:

Number of participants with positive ADA titer to MEDI4736 are reported. ADA incidence is defined as either treatment-induced (post baseline ADA-positive only) or treatment-boosted ADA; treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to a 4-fold or higher level following drug administration; persistent positive is defined as positive at >= 2 post-baseline assessments (with >= 16 weeks between first and last positive) or positive at last post-baseline assessment; and transient positive is defined as having at least one post-baseline ADA-positive assessment and not fulfilling the condition of persistent positive. The ADA evaluable population included all participants who received at least 1 dose of MEDI4736 and had any post-dose ADA data point was considered for this endpoint.

End point type	Secondary

End point timeframe:

Escalation part: Days 1, 29, 85, 141, 169, 253, and 337, end of treatment (EOT), 90 days post EOT, and 6 months post last dose; Expansion part: Days 1, 85, and 169, EOT, 90 days post EOT, and 6 months post last dose (approximately 6 years)

End point values	Escalation MEDI4736 Dose 1 (Q4W)	Escalation MEDI4736 Dose 2 (Q4W)	Escalation MEDI4736 Dose 3 (Q4W)	Escalation & Expansion MEDI4736 Dose 4 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	3	5	35	247
Units: Participants				
ADA incidence	0	1	4	5

Treatment-boosted ADA	0	0	2	0
Persistent positive	0	1	4	6
Transient positive	0	0	0	0

End point values	Escalation MEDI4736 Dose 2 (Q2W)			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Participants				
ADA incidence	1			
Treatment-boosted ADA	0			
Persistent positive	1			
Transient positive	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Positive ADA to Tremelimumab

End point title	Number of Participants With Positive ADA to Tremelimumab

End point description:

Number of participants with positive ADA titer to tremelimumab are reported. ADA incidence is defined as either treatment-induced (post baseline ADA-positive only) or treatment-boosted ADA; treatment-boosted ADA is defined as baseline positive ADA titer that was boosted to a 4-fold or higher level following drug administration; persistent positive is defined as positive at >= 2 post-baseline assessments (with >= 16 weeks between first and last positive) or positive at last post-baseline assessment; and transient positive is defined as having at least one post-baseline ADA-positive assessment and not fulfilling the condition of persistent positive. The ADA evaluable population included all participants who received at least 1 dose of tremelimumab and had any post-dose ADA data point was considered for this endpoint.

End point type	Secondary

End point timeframe:

Escalation part: Days 1, 29, 85, 141, 169, 253, and 337, end of treatment (EOT), 90 days post EOT, and 6 months post last dose; Expansion part: Days 1, 85, and 169, EOT, 90 days post EOT, and 6 months post last dose (approximately 6 years)

End point values	Escalation Tremelimumab Dose 3 (Q4W)	Escalation Tremelimumab Dose 1 (Q4W)	Escalation Tremelimumab Dose 2 (Q4W)	Expansion Tremelimumab Dose 1 (Q4W)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9	47	28	211
Units: Participants				
ADA incidence	0	6	1	14
Treatment-boosted ADA	0	0	0	0
Persistent positive	0	3	0	8
Transient positive	0	3	1	6

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Programmed Cell Death Ligand 1 (PD-L1) Disposition in Cohort B (Sequential Administration)

End point title	Number of Participants With Programmed Cell Death Ligand 1 (PD-L1) Disposition in Cohort B (Sequential Administration)[26]

End point description:

Number of participants with PD-L1 disposition are reported. It is reported as tumour cells disposition high (>=25%) and low/negative (<25%). As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) were considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants for whom a PD-L1 status was obtained.

End point type	Secondary

End point timeframe:

Screening (Days -28 to -1), Day 50, Day 225

Notes:

[26] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)			
Subject group type	Reporting group			
Number of subjects analysed	193			
Units: Participants				
Tumour cells high (TC>=25%)	57			
Tumour cells low/negative (TC<25%)	136			

Statistical analyses

No statistical analyses for this end point

Secondary: Cluster of differentiation (CD) 8 Cell densities in Cohort B (Sequential Administration)

End point title	Cluster of differentiation (CD) 8 Cell densities in Cohort B (Sequential Administration)[27]

End point description:

CD8 Cell densities are reported. As-treated population included all participants who received any dose of study drugs (MEDI4736 or tremelimumab) were considered for this endpoint. The "Number of Subjects Analysed" denotes the number of participants for whom CD8 cell density was obtained.

End point type	Secondary

End point timeframe:

Screening (Days -28 to -1), Day 50, Day 225

Notes:

[27] - 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: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Expansion Cohort B (Sequential)			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: Cells/mm^2				
arithmetic mean (standard deviation)	357.7 (± 373.8)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 through 90 days after the last dose of study drug (approximately 6 years)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Total Escalation

Reporting group description:

Participants received MEDI4736 IV escalation doses (Dose 1 or 2 or 3 or 4) every 4 weeks (Q4W; up to 13 doses) or every two weeks (Q2W; up to 26 doses) and IV tremelimumab dose (Dose 1, 2, or 3) Q4W for 6 doses and then every 12 weeks (Q12W) for 3 doses (up to 9 doses in total) for 12 months or until disease progression.

Reporting group title	Expansion Cohort A

Reporting group description:

Treatment-naïve, non-epidermal growth factor receptor (non-EGFR) mutation positive, and non-anaplastic lymphoma kinase (non-ALK) rearrangement positive participants received IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.

Reporting group title	Expansion Cohort B (Coadmin)

Reporting group description:

Immunotherapy-naive participants received co-administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.

Reporting group title	Expansion Cohort B (Sequential)

Reporting group description:

Immunotherapy-naive participants received sequential administration of IV MEDI4736 Dose 4 Q4W and IV tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W monotherapy for 9 doses to complete a total of 12 months of therapy or until disease progression.

Reporting group title	Expansion Cohort C (Refractory)

Reporting group description:

Participants who were refractory to previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy or until disease progression.

Reporting group title	Expansion Cohort C (Relapsed)

Reporting group description:

Participants whom disease was relapsed with the previous immunotherapy treatment received IV infusion of MEDI4736 Dose 4 Q4W and tremelimumab Dose 1 Q4W for up to 4 doses each, followed by monotherapy with IV MEDI4736 Dose 4 Q4W for 9 doses to complete a total of 12 months of therapy.

Serious adverse events	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 102 (66.67%)	20 / 45 (44.44%)	11 / 19 (57.89%)
number of deaths (all causes)	66	24	15
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extradural neoplasm			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Malignant neoplasm progression			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Malignant pleural effusion			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			

subjects affected / exposed	11 / 102 (10.78%)	5 / 45 (11.11%)	3 / 19 (15.79%)
occurrences causally related to treatment / all	0 / 14	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 10	0 / 3	0 / 3
Non-small cell lung cancer metastatic			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis malignant			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer stage IV			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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			
Deep vein thrombosis			

subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Embolism			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular compression			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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			
Asthenia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Chest pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	4 / 102 (3.92%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			

subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	4 / 102 (3.92%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 respiratory failure			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Aspiration			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Bronchial disorder			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Bronchial obstruction			

subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	0 / 19 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	6 / 102 (5.88%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Hypoxia			
subjects affected / exposed	3 / 102 (2.94%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	1 / 102 (0.98%)	1 / 45 (2.22%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 aspiration			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	5 / 102 (4.90%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 102 (0.00%)	2 / 45 (4.44%)	0 / 19 (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 / 102 (0.98%)	2 / 45 (4.44%)	3 / 19 (15.79%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
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 failure			
subjects affected / exposed	2 / 102 (1.96%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Mental status changes			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 malfunction			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Liver function test increased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Lymphocyte count decreased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Oxygen saturation decreased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Platelet count decreased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Femur fracture			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Hip fracture			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Infusion related reaction			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Radiation pneumonitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Spinal compression fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Spinal fracture			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute left ventricular failure			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 102 (0.98%)	2 / 45 (4.44%)	4 / 19 (21.05%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Congestive cardiomyopathy			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Myocarditis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Pericardial effusion			
subjects affected / exposed	2 / 102 (1.96%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Sinus tachycardia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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			
Brain oedema			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Central nervous system haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system lesion			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Depressed level of consciousness			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Dysarthria			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Encephalopathy			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Headache			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Intercostal neuralgia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Metabolic encephalopathy			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Myasthenia gravis			

subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Neuromyopathy			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Spinal cord compression			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	0 / 19 (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
Tension headache			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Tremor			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Vasogenic cerebral oedema			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Febrile neutropenia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Hypocoagulable state			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Splenic haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	1 / 102 (0.98%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Abdominal pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Abdominal pain upper			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 colitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	10 / 102 (9.80%)	4 / 45 (8.89%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	12 / 12	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 102 (0.98%)	2 / 45 (4.44%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	10 / 102 (9.80%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	10 / 11	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Enterocolitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 perforation			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Impaired gastric emptying			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Large intestine perforation			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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 gastrointestinal haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	3 / 19 (15.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Pneumoperitoneum			

subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Retroperitoneal haematoma			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 / 102 (0.00%)	2 / 45 (4.44%)	0 / 19 (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
Vomiting			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Bile duct obstruction			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Hepatic function abnormal			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Hyperbilirubinaemia			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Purpura			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Rash maculo-papular			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 102 (0.98%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Adrenal insufficiency			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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

Hyperthyroidism			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Hypophysitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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			
Arthralgia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Back pain			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Bone pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Muscular weakness			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal chest pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 pain			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Myositis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Neck pain			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Paraneoplastic arthritis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Pathological fracture			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Polymyositis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Rhabdomyolysis			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Spinal stenosis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	1 / 102 (0.98%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Diverticulitis			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	0 / 19 (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
Enterocolitis infectious			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Influenza			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 viral			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Lung infection			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 102 (2.94%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Proteus infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 acute			

subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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 syncytial virus infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 102 (1.96%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Soft tissue infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Streptococcal sepsis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Tracheobronchitis viral			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (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
Urinary tract infection			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Urosepsis			

subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	5 / 102 (4.90%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	2 / 5	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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	3 / 102 (2.94%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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
Hyperuricaemia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (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
Hypoglycaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (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	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)
Total subjects affected by serious adverse events			
subjects affected / exposed	120 / 213 (56.34%)	26 / 38 (68.42%)	22 / 40 (55.00%)
number of deaths (all causes)	126	28	31
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Extradural neoplasm			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 213 (0.47%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	10 / 213 (4.69%)	1 / 38 (2.63%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 15	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 8	0 / 0	0 / 2

Malignant neoplasm progression			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Malignant pleural effusion			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Metastases to central nervous system			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	47 / 213 (22.07%)	7 / 38 (18.42%)	7 / 40 (17.50%)
occurrences causally related to treatment / all	0 / 61	0 / 9	0 / 11
deaths causally related to treatment / all	0 / 29	0 / 6	0 / 7
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 213 (0.47%)	1 / 38 (2.63%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Pericarditis malignant			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			

subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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-small cell lung cancer stage IV			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Embolism			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Hypertension			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 compression			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	4 / 213 (1.88%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	1 / 213 (0.47%)	1 / 38 (2.63%)	0 / 40 (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
Oedema peripheral			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Pyrexia			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Acute respiratory failure			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Bronchial disorder			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Bronchial obstruction			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Dyspnoea			
subjects affected / exposed	8 / 213 (3.76%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Haemothorax			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Hypoxia			

subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	6 / 213 (2.82%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	4 / 213 (1.88%)	2 / 38 (5.26%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	4 / 4	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	2 / 213 (0.94%)	2 / 38 (5.26%)	3 / 40 (7.50%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			

subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 failure			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Mental status changes			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Product issues			
Device malfunction			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Amylase increased			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 alkaline phosphatase increased			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Lipase increased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Liver function test increased			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Oxygen saturation decreased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Platelet count decreased			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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			
Fall			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Hip fracture			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Humerus fracture			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Infusion related reaction			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radiation pneumonitis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Radius fracture			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Spinal compression fracture			

subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Spinal fracture			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 left ventricular failure			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 tamponade			

subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Congestive cardiomyopathy			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Myocarditis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Pericardial effusion			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Sinus tachycardia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Central nervous system haemorrhage			

subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Central nervous system lesion			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 ischaemia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Depressed level of consciousness			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Dysarthria			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Encephalopathy			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Hydrocephalus			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intercostal neuralgia			

subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Metabolic encephalopathy			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Myasthenia gravis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Neuromyopathy			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Paraesthesia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Seizure			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Spinal cord compression			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			

subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Tremor			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Vasogenic cerebral oedema			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Hypocoagulable state			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Splenic haemorrhage			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal mass			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	3 / 213 (1.41%)	1 / 38 (2.63%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Autoimmune colitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	6 / 213 (2.82%)	1 / 38 (2.63%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	7 / 7	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Diarrhoea			
subjects affected / exposed	5 / 213 (2.35%)	1 / 38 (2.63%)	3 / 40 (7.50%)
occurrences causally related to treatment / all	5 / 6	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Enterocolitis			

subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Faecaloma			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Gastrointestinal perforation			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Impaired gastric emptying			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Large intestine perforation			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Nausea			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal stenosis			

subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Retroperitoneal haematoma			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Vomiting			
subjects affected / exposed	2 / 213 (0.94%)	1 / 38 (2.63%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Bile duct obstruction			

subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Purpura			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Rash maculo-papular			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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			
Acute kidney injury			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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	2 / 213 (0.94%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Muscular weakness			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 chest pain			
subjects affected / exposed	1 / 213 (0.47%)	1 / 38 (2.63%)	0 / 40 (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
Musculoskeletal pain			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Myositis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Neck pain			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Paraneoplastic arthritis			

subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Pathological fracture			
subjects affected / exposed	2 / 213 (0.94%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyositis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Rhabdomyolysis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Spinal stenosis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Device related infection			

subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Lung infection			
subjects affected / exposed	6 / 213 (2.82%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	13 / 213 (6.10%)	7 / 38 (18.42%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 14	1 / 7	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteus infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Pyelonephritis acute			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	1 / 213 (0.47%)	1 / 38 (2.63%)	0 / 40 (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
Septic shock			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Streptococcal sepsis			

subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Tracheobronchitis viral			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Urinary tract infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	0 / 40 (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
Urosepsis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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			
Decreased appetite			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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	4 / 213 (1.88%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Hyperkalaemia			

subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Hyperuricaemia			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (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
Hypoglycaemia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (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

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

Non-serious adverse events	Total Escalation	Expansion Cohort A	Expansion Cohort B (Coadmin)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 102 (96.08%)	44 / 45 (97.78%)	18 / 19 (94.74%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Hypertension			
subjects affected / exposed	6 / 102 (5.88%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences (all)	6	1	0
Hypotension			
subjects affected / exposed	5 / 102 (4.90%)	1 / 45 (2.22%)	3 / 19 (15.79%)
occurrences (all)	6	1	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 102 (5.88%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences (all)	6	0	4
Chills			
subjects affected / exposed	5 / 102 (4.90%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences (all)	5	2	1
Fatigue			
subjects affected / exposed	35 / 102 (34.31%)	15 / 45 (33.33%)	8 / 19 (42.11%)
occurrences (all)	62	21	13
Influenza like illness			
subjects affected / exposed	6 / 102 (5.88%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	6	0	0
Malaise			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Non-cardiac chest pain			
subjects affected / exposed	1 / 102 (0.98%)	4 / 45 (8.89%)	0 / 19 (0.00%)
occurrences (all)	1	4	0
Oedema			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	4	0	1
Oedema peripheral			
subjects affected / exposed	11 / 102 (10.78%)	11 / 45 (24.44%)	0 / 19 (0.00%)
occurrences (all)	12	12	0
Pyrexia			

subjects affected / exposed	17 / 102 (16.67%)	4 / 45 (8.89%)	2 / 19 (10.53%)
occurrences (all)	20	4	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Cough			
subjects affected / exposed	19 / 102 (18.63%)	10 / 45 (22.22%)	4 / 19 (21.05%)
occurrences (all)	23	13	5
Dry throat			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Dyspnoea			
subjects affected / exposed	20 / 102 (19.61%)	18 / 45 (40.00%)	6 / 19 (31.58%)
occurrences (all)	27	35	8
Dyspnoea exertional			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Haemoptysis			
subjects affected / exposed	1 / 102 (0.98%)	3 / 45 (6.67%)	0 / 19 (0.00%)
occurrences (all)	1	4	0
Hypoxia			
subjects affected / exposed	4 / 102 (3.92%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences (all)	4	2	1
Laryngeal haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nasal congestion			

subjects affected / exposed	6 / 102 (5.88%)	5 / 45 (11.11%)	1 / 19 (5.26%)
occurrences (all)	7	5	1
Oropharyngeal pain			
subjects affected / exposed	1 / 102 (0.98%)	3 / 45 (6.67%)	0 / 19 (0.00%)
occurrences (all)	1	3	0
Pleural effusion			
subjects affected / exposed	0 / 102 (0.00%)	2 / 45 (4.44%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Pneumonitis			
subjects affected / exposed	1 / 102 (0.98%)	3 / 45 (6.67%)	0 / 19 (0.00%)
occurrences (all)	2	4	0
Productive cough			
subjects affected / exposed	8 / 102 (7.84%)	5 / 45 (11.11%)	1 / 19 (5.26%)
occurrences (all)	9	5	1
Wheezing			
subjects affected / exposed	2 / 102 (1.96%)	6 / 45 (13.33%)	1 / 19 (5.26%)
occurrences (all)	3	11	1
Pulmonary embolism			
subjects affected / exposed	4 / 102 (3.92%)	2 / 45 (4.44%)	0 / 19 (0.00%)
occurrences (all)	4	2	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 102 (7.84%)	3 / 45 (6.67%)	2 / 19 (10.53%)
occurrences (all)	8	3	2
Depression			
subjects affected / exposed	3 / 102 (2.94%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Insomnia			
subjects affected / exposed	8 / 102 (7.84%)	5 / 45 (11.11%)	2 / 19 (10.53%)
occurrences (all)	10	8	2
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	3
Alanine aminotransferase increased			

subjects affected / exposed	13 / 102 (12.75%)	4 / 45 (8.89%)	1 / 19 (5.26%)
occurrences (all)	19	4	1
Amylase increased			
subjects affected / exposed	19 / 102 (18.63%)	8 / 45 (17.78%)	1 / 19 (5.26%)
occurrences (all)	23	14	2
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 102 (9.80%)	2 / 45 (4.44%)	2 / 19 (10.53%)
occurrences (all)	18	2	2
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 102 (3.92%)	3 / 45 (6.67%)	3 / 19 (15.79%)
occurrences (all)	6	3	3
Blood cholesterol increased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	11 / 102 (10.78%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	20	1	2
Blood fibrinogen increased			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	6 / 102 (5.88%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences (all)	6	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	7 / 102 (6.86%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	7	3	1
Blood triglycerides increased			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 102 (9.80%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	14	1	1
International normalised ratio increased			

subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Lipase increased			
subjects affected / exposed	15 / 102 (14.71%)	6 / 45 (13.33%)	3 / 19 (15.79%)
occurrences (all)	23	7	3
Transaminases increased			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Weight decreased			
subjects affected / exposed	6 / 102 (5.88%)	4 / 45 (8.89%)	3 / 19 (15.79%)
occurrences (all)	6	4	4
Lymphocyte count decreased			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences (all)	1	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Head injury			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	1	1	2
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Sinus tachycardia			
subjects affected / exposed	5 / 102 (4.90%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences (all)	6	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 102 (9.80%)	4 / 45 (8.89%)	0 / 19 (0.00%)
occurrences (all)	11	5	0
Dysgeusia			

subjects affected / exposed	5 / 102 (4.90%)	4 / 45 (8.89%)	0 / 19 (0.00%)
occurrences (all)	5	4	0
Headache			
subjects affected / exposed	12 / 102 (11.76%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	18	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Seizure			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Visual field defect			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Neuropathy peripheral			
subjects affected / exposed	3 / 102 (2.94%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 102 (19.61%)	5 / 45 (11.11%)	2 / 19 (10.53%)
occurrences (all)	30	9	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 102 (7.84%)	3 / 45 (6.67%)	3 / 19 (15.79%)
occurrences (all)	10	3	6
Abdominal pain upper			
subjects affected / exposed	5 / 102 (4.90%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	6	0	1
Constipation			
subjects affected / exposed	13 / 102 (12.75%)	12 / 45 (26.67%)	4 / 19 (21.05%)
occurrences (all)	13	16	4
Diarrhoea			
subjects affected / exposed	42 / 102 (41.18%)	13 / 45 (28.89%)	8 / 19 (42.11%)
occurrences (all)	89	22	14
Dry mouth			

subjects affected / exposed	8 / 102 (7.84%)	6 / 45 (13.33%)	2 / 19 (10.53%)
occurrences (all)	8	6	2
Enterocolitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	27 / 102 (26.47%)	12 / 45 (26.67%)	4 / 19 (21.05%)
occurrences (all)	30	17	6
Stomatitis			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Vomiting			
subjects affected / exposed	15 / 102 (14.71%)	6 / 45 (13.33%)	2 / 19 (10.53%)
occurrences (all)	19	9	3
Colitis			
subjects affected / exposed	4 / 102 (3.92%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences (all)	6	1	0
Flatulence			
subjects affected / exposed	3 / 102 (2.94%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Hyperbilirubinaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	6 / 102 (5.88%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences (all)	8	2	1
Night sweats			
subjects affected / exposed	2 / 102 (1.96%)	3 / 45 (6.67%)	0 / 19 (0.00%)
occurrences (all)	2	3	0
Pruritus			

subjects affected / exposed	26 / 102 (25.49%)	9 / 45 (20.00%)	0 / 19 (0.00%)
occurrences (all)	41	13	0
Rash			
subjects affected / exposed	22 / 102 (21.57%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences (all)	37	2	1
Rash macular			
subjects affected / exposed	0 / 102 (0.00%)	3 / 45 (6.67%)	0 / 19 (0.00%)
occurrences (all)	0	4	0
Rash maculo-papular			
subjects affected / exposed	9 / 102 (8.82%)	11 / 45 (24.44%)	1 / 19 (5.26%)
occurrences (all)	13	12	1
Urticaria			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Haematuria			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Micturition urgency			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Pollakiuria			
subjects affected / exposed	1 / 102 (0.98%)	3 / 45 (6.67%)	1 / 19 (5.26%)
occurrences (all)	1	3	1
Polyuria			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	5 / 102 (4.90%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	8	1	1
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	4 / 102 (3.92%)	2 / 45 (4.44%)	2 / 19 (10.53%)
occurrences (all)	4	2	2
Hypothyroidism			
subjects affected / exposed	12 / 102 (11.76%)	1 / 45 (2.22%)	3 / 19 (15.79%)
occurrences (all)	13	3	3
Adrenal insufficiency			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 102 (12.75%)	6 / 45 (13.33%)	1 / 19 (5.26%)
occurrences (all)	19	10	1
Back pain			
subjects affected / exposed	10 / 102 (9.80%)	7 / 45 (15.56%)	4 / 19 (21.05%)
occurrences (all)	14	9	5
Bone pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	9 / 102 (8.82%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	9	2	2
Muscular weakness			
subjects affected / exposed	4 / 102 (3.92%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences (all)	5	2	1
Musculoskeletal chest pain			
subjects affected / exposed	10 / 102 (9.80%)	6 / 45 (13.33%)	0 / 19 (0.00%)
occurrences (all)	11	9	0
Musculoskeletal pain			
subjects affected / exposed	7 / 102 (6.86%)	1 / 45 (2.22%)	0 / 19 (0.00%)
occurrences (all)	9	1	0
Myalgia			
subjects affected / exposed	5 / 102 (4.90%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	7	1	1
Neck pain			

subjects affected / exposed	5 / 102 (4.90%)	1 / 45 (2.22%)	2 / 19 (10.53%)
occurrences (all)	5	2	2
Pain in extremity			
subjects affected / exposed	7 / 102 (6.86%)	3 / 45 (6.67%)	1 / 19 (5.26%)
occurrences (all)	8	4	1
Pain in jaw			
subjects affected / exposed	1 / 102 (0.98%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 102 (2.94%)	3 / 45 (6.67%)	0 / 19 (0.00%)
occurrences (all)	4	6	0
Candida infection			
subjects affected / exposed	0 / 102 (0.00%)	1 / 45 (2.22%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Lung infection			
subjects affected / exposed	3 / 102 (2.94%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	3	1	2
Oral candidiasis			
subjects affected / exposed	3 / 102 (2.94%)	1 / 45 (2.22%)	1 / 19 (5.26%)
occurrences (all)	3	1	1
Pharyngitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	3 / 102 (2.94%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Sinusitis			
subjects affected / exposed	3 / 102 (2.94%)	3 / 45 (6.67%)	0 / 19 (0.00%)
occurrences (all)	3	3	0
Upper respiratory tract infection			
subjects affected / exposed	5 / 102 (4.90%)	5 / 45 (11.11%)	1 / 19 (5.26%)
occurrences (all)	5	6	1
Urinary tract infection			
subjects affected / exposed	6 / 102 (5.88%)	4 / 45 (8.89%)	0 / 19 (0.00%)
occurrences (all)	8	4	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 102 (20.59%)	10 / 45 (22.22%)	6 / 19 (31.58%)
occurrences (all)	25	12	8
Dehydration			
subjects affected / exposed	5 / 102 (4.90%)	1 / 45 (2.22%)	2 / 19 (10.53%)
occurrences (all)	11	1	2
Hyperglycaemia			
subjects affected / exposed	10 / 102 (9.80%)	3 / 45 (6.67%)	2 / 19 (10.53%)
occurrences (all)	21	5	2
Hyperkalaemia			
subjects affected / exposed	2 / 102 (1.96%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences (all)	2	2	3
Hypertriglyceridaemia			
subjects affected / exposed	2 / 102 (1.96%)	0 / 45 (0.00%)	2 / 19 (10.53%)
occurrences (all)	4	0	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 102 (0.00%)	3 / 45 (6.67%)	2 / 19 (10.53%)
occurrences (all)	0	3	2
Hypocalcaemia			
subjects affected / exposed	1 / 102 (0.98%)	2 / 45 (4.44%)	1 / 19 (5.26%)
occurrences (all)	1	2	1
Hypoglycaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 45 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	5 / 102 (4.90%)	5 / 45 (11.11%)	1 / 19 (5.26%)
occurrences (all)	8	6	1
Hypomagnesaemia			
subjects affected / exposed	8 / 102 (7.84%)	2 / 45 (4.44%)	0 / 19 (0.00%)
occurrences (all)	9	2	0
Hyponatraemia			
subjects affected / exposed	7 / 102 (6.86%)	5 / 45 (11.11%)	2 / 19 (10.53%)
occurrences (all)	11	5	2

Non-serious adverse events	Expansion Cohort B (Sequential)	Expansion Cohort C (Refractory)	Expansion Cohort C (Relapsed)

Total subjects affected by non-serious adverse events			
subjects affected / exposed	208 / 213 (97.65%)	35 / 38 (92.11%)	38 / 40 (95.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	4 / 213 (1.88%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	4	2	1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 213 (1.41%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Hypertension			
subjects affected / exposed	5 / 213 (2.35%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	17	2	3
Hypotension			
subjects affected / exposed	11 / 213 (5.16%)	1 / 38 (2.63%)	3 / 40 (7.50%)
occurrences (all)	15	1	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 213 (21.60%)	1 / 38 (2.63%)	3 / 40 (7.50%)
occurrences (all)	85	1	5
Chills			
subjects affected / exposed	8 / 213 (3.76%)	2 / 38 (5.26%)	2 / 40 (5.00%)
occurrences (all)	8	2	2
Fatigue			
subjects affected / exposed	63 / 213 (29.58%)	14 / 38 (36.84%)	13 / 40 (32.50%)
occurrences (all)	96	15	15
Influenza like illness			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	3	0	1
Malaise			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	3	0	1
Non-cardiac chest pain			
subjects affected / exposed	16 / 213 (7.51%)	2 / 38 (5.26%)	2 / 40 (5.00%)
occurrences (all)	17	3	2
Oedema			

subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	2
Oedema peripheral			
subjects affected / exposed	18 / 213 (8.45%)	2 / 38 (5.26%)	4 / 40 (10.00%)
occurrences (all)	22	2	4
Pyrexia			
subjects affected / exposed	31 / 213 (14.55%)	4 / 38 (10.53%)	2 / 40 (5.00%)
occurrences (all)	33	4	3
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	4 / 213 (1.88%)	2 / 38 (5.26%)	0 / 40 (0.00%)
occurrences (all)	4	2	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 213 (0.94%)	2 / 38 (5.26%)	0 / 40 (0.00%)
occurrences (all)	2	3	0
Cough			
subjects affected / exposed	39 / 213 (18.31%)	8 / 38 (21.05%)	7 / 40 (17.50%)
occurrences (all)	46	8	9
Dry throat			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Dyspnoea			
subjects affected / exposed	59 / 213 (27.70%)	10 / 38 (26.32%)	11 / 40 (27.50%)
occurrences (all)	80	18	12
Dyspnoea exertional			
subjects affected / exposed	8 / 213 (3.76%)	0 / 38 (0.00%)	4 / 40 (10.00%)
occurrences (all)	9	0	4
Haemoptysis			
subjects affected / exposed	15 / 213 (7.04%)	3 / 38 (7.89%)	1 / 40 (2.50%)
occurrences (all)	18	3	2
Hypoxia			

subjects affected / exposed	3 / 213 (1.41%)	2 / 38 (5.26%)	2 / 40 (5.00%)
occurrences (all)	3	2	2
Laryngeal haemorrhage			
subjects affected / exposed	2 / 213 (0.94%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Nasal congestion			
subjects affected / exposed	3 / 213 (1.41%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	3	2	1
Oropharyngeal pain			
subjects affected / exposed	6 / 213 (2.82%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	6	1	0
Pleural effusion			
subjects affected / exposed	9 / 213 (4.23%)	4 / 38 (10.53%)	1 / 40 (2.50%)
occurrences (all)	14	6	1
Pneumonitis			
subjects affected / exposed	5 / 213 (2.35%)	1 / 38 (2.63%)	3 / 40 (7.50%)
occurrences (all)	5	1	4
Productive cough			
subjects affected / exposed	14 / 213 (6.57%)	5 / 38 (13.16%)	1 / 40 (2.50%)
occurrences (all)	15	6	1
Wheezing			
subjects affected / exposed	4 / 213 (1.88%)	3 / 38 (7.89%)	1 / 40 (2.50%)
occurrences (all)	4	3	2
Pulmonary embolism			
subjects affected / exposed	4 / 213 (1.88%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	4	0	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 213 (3.76%)	3 / 38 (7.89%)	1 / 40 (2.50%)
occurrences (all)	8	3	1
Depression			
subjects affected / exposed	11 / 213 (5.16%)	3 / 38 (7.89%)	1 / 40 (2.50%)
occurrences (all)	12	3	1
Insomnia			
subjects affected / exposed	17 / 213 (7.98%)	4 / 38 (10.53%)	2 / 40 (5.00%)
occurrences (all)	18	4	2

Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	3 / 213 (1.41%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Alanine aminotransferase increased			
subjects affected / exposed	15 / 213 (7.04%)	0 / 38 (0.00%)	3 / 40 (7.50%)
occurrences (all)	23	0	3
Amylase increased			
subjects affected / exposed	28 / 213 (13.15%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	65	3	2
Aspartate aminotransferase increased			
subjects affected / exposed	17 / 213 (7.98%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	22	0	3
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 213 (3.76%)	1 / 38 (2.63%)	3 / 40 (7.50%)
occurrences (all)	12	1	5
Blood cholesterol increased			
subjects affected / exposed	4 / 213 (1.88%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Blood creatinine increased			
subjects affected / exposed	8 / 213 (3.76%)	2 / 38 (5.26%)	3 / 40 (7.50%)
occurrences (all)	15	2	5
Blood fibrinogen increased			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	7 / 213 (3.29%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	7	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood triglycerides increased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	3 / 40 (7.50%)
occurrences (all)	1	0	3

Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 213 (4.69%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	14	2	1
International normalised ratio increased			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Lipase increased			
subjects affected / exposed	16 / 213 (7.51%)	1 / 38 (2.63%)	4 / 40 (10.00%)
occurrences (all)	44	4	8
Transaminases increased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	19 / 213 (8.92%)	5 / 38 (13.16%)	5 / 40 (12.50%)
occurrences (all)	23	6	5
Lymphocyte count decreased			
subjects affected / exposed	5 / 213 (2.35%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	5	0	2
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 213 (1.41%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Head injury			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	13 / 213 (6.10%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	16	0	3
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	2 / 213 (0.94%)	1 / 38 (2.63%)	2 / 40 (5.00%)
occurrences (all)	2	1	3

Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 213 (8.45%)	2 / 38 (5.26%)	5 / 40 (12.50%)
occurrences (all)	24	2	5
Dysgeusia			
subjects affected / exposed	6 / 213 (2.82%)	1 / 38 (2.63%)	1 / 40 (2.50%)
occurrences (all)	6	1	1
Headache			
subjects affected / exposed	17 / 213 (7.98%)	1 / 38 (2.63%)	3 / 40 (7.50%)
occurrences (all)	21	1	3
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	6 / 213 (2.82%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	6	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	40 / 213 (18.78%)	2 / 38 (5.26%)	6 / 40 (15.00%)
occurrences (all)	70	5	12
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	25 / 213 (11.74%)	3 / 38 (7.89%)	5 / 40 (12.50%)
occurrences (all)	27	3	5
Abdominal pain upper			
subjects affected / exposed	6 / 213 (2.82%)	1 / 38 (2.63%)	2 / 40 (5.00%)
occurrences (all)	6	1	2
Constipation			
subjects affected / exposed	44 / 213 (20.66%)	4 / 38 (10.53%)	12 / 40 (30.00%)
occurrences (all)	59	4	13
Diarrhoea			

subjects affected / exposed	49 / 213 (23.00%)	10 / 38 (26.32%)	13 / 40 (32.50%)
occurrences (all)	76	14	22
Dry mouth			
subjects affected / exposed	17 / 213 (7.98%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	20	1	0
Enterocolitis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	39 / 213 (18.31%)	9 / 38 (23.68%)	9 / 40 (22.50%)
occurrences (all)	50	11	10
Stomatitis			
subjects affected / exposed	9 / 213 (4.23%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	9	0	1
Vomiting			
subjects affected / exposed	20 / 213 (9.39%)	8 / 38 (21.05%)	8 / 40 (20.00%)
occurrences (all)	23	9	10
Colitis			
subjects affected / exposed	5 / 213 (2.35%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	6	0	2
Flatulence			
subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	4	0	2
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	12 / 213 (5.63%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	15	2	1
Night sweats			

subjects affected / exposed	2 / 213 (0.94%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
Pruritus			
subjects affected / exposed	44 / 213 (20.66%)	8 / 38 (21.05%)	5 / 40 (12.50%)
occurrences (all)	64	9	7
Rash			
subjects affected / exposed	35 / 213 (16.43%)	4 / 38 (10.53%)	2 / 40 (5.00%)
occurrences (all)	49	4	3
Rash macular			
subjects affected / exposed	1 / 213 (0.47%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
Rash maculo-papular			
subjects affected / exposed	6 / 213 (2.82%)	3 / 38 (7.89%)	1 / 40 (2.50%)
occurrences (all)	7	3	3
Urticaria			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	3	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	4 / 213 (1.88%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Micturition urgency			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Polyuria			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1

Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	23 / 213 (10.80%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	32	0	1
Hypothyroidism			
subjects affected / exposed	27 / 213 (12.68%)	4 / 38 (10.53%)	3 / 40 (7.50%)
occurrences (all)	32	4	3
Adrenal insufficiency			
subjects affected / exposed	2 / 213 (0.94%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	2	0	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 213 (16.90%)	3 / 38 (7.89%)	9 / 40 (22.50%)
occurrences (all)	55	3	15
Back pain			
subjects affected / exposed	31 / 213 (14.55%)	3 / 38 (7.89%)	2 / 40 (5.00%)
occurrences (all)	37	3	2
Bone pain			
subjects affected / exposed	7 / 213 (3.29%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	9	0	1
Muscle spasms			
subjects affected / exposed	4 / 213 (1.88%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Muscular weakness			
subjects affected / exposed	8 / 213 (3.76%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	10	0	1
Musculoskeletal chest pain			
subjects affected / exposed	15 / 213 (7.04%)	4 / 38 (10.53%)	5 / 40 (12.50%)
occurrences (all)	16	4	7
Musculoskeletal pain			
subjects affected / exposed	19 / 213 (8.92%)	3 / 38 (7.89%)	1 / 40 (2.50%)
occurrences (all)	20	5	1
Myalgia			
subjects affected / exposed	14 / 213 (6.57%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	15	0	1
Neck pain			

subjects affected / exposed	3 / 213 (1.41%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	5	0	0
Pain in extremity			
subjects affected / exposed	9 / 213 (4.23%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	10	1	0
Pain in jaw			
subjects affected / exposed	0 / 213 (0.00%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 213 (1.41%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	4	3	1
Candida infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 38 (2.63%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Lung infection			
subjects affected / exposed	9 / 213 (4.23%)	0 / 38 (0.00%)	2 / 40 (5.00%)
occurrences (all)	11	0	4
Oral candidiasis			
subjects affected / exposed	8 / 213 (3.76%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	8	1	0
Pharyngitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 38 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	10 / 213 (4.69%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	10	2	1
Sinusitis			
subjects affected / exposed	4 / 213 (1.88%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	5	0	1
Upper respiratory tract infection			
subjects affected / exposed	17 / 213 (7.98%)	2 / 38 (5.26%)	3 / 40 (7.50%)
occurrences (all)	21	2	4
Urinary tract infection			
subjects affected / exposed	7 / 213 (3.29%)	2 / 38 (5.26%)	1 / 40 (2.50%)
occurrences (all)	7	2	1

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	61 / 213 (28.64%)	8 / 38 (21.05%)	9 / 40 (22.50%)
occurrences (all)	84	9	10
Dehydration			
subjects affected / exposed	6 / 213 (2.82%)	3 / 38 (7.89%)	2 / 40 (5.00%)
occurrences (all)	7	3	2
Hyperglycaemia			
subjects affected / exposed	11 / 213 (5.16%)	2 / 38 (5.26%)	4 / 40 (10.00%)
occurrences (all)	15	5	4
Hyperkalaemia			
subjects affected / exposed	7 / 213 (3.29%)	1 / 38 (2.63%)	2 / 40 (5.00%)
occurrences (all)	10	1	4
Hypertriglyceridaemia			
subjects affected / exposed	7 / 213 (3.29%)	1 / 38 (2.63%)	2 / 40 (5.00%)
occurrences (all)	7	1	2
Hypoalbuminaemia			
subjects affected / exposed	7 / 213 (3.29%)	0 / 38 (0.00%)	3 / 40 (7.50%)
occurrences (all)	12	0	6
Hypocalcaemia			
subjects affected / exposed	5 / 213 (2.35%)	0 / 38 (0.00%)	1 / 40 (2.50%)
occurrences (all)	5	0	1
Hypoglycaemia			
subjects affected / exposed	3 / 213 (1.41%)	1 / 38 (2.63%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Hypokalaemia			
subjects affected / exposed	11 / 213 (5.16%)	3 / 38 (7.89%)	7 / 40 (17.50%)
occurrences (all)	17	4	10
Hypomagnesaemia			
subjects affected / exposed	4 / 213 (1.88%)	5 / 38 (13.16%)	2 / 40 (5.00%)
occurrences (all)	5	5	3
Hyponatraemia			
subjects affected / exposed	11 / 213 (5.16%)	5 / 38 (13.16%)	3 / 40 (7.50%)
occurrences (all)	17	7	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2013	Updated exclusion criteria for participants with non-small cell lung cancer with tumors harboring anaplastic lymphoma kinase gene rearrangements or epidermal growth factor receptor sensitizing mutations, and added dose-limiting toxicity criteria for any pneumonitis.
19 December 2013	The synopsis was updated to match the body of the protocol. The clinical summary sections were updated. Updated the DLT evaluation period and added the rationale for DLT period.
29 May 2014	Removed immunotherapy pretreated cohorts. Added Q2W dosing schedule. Updated primary objectives for dosing schedule information, secondary objectives for the antitumor objective to specify RECIST version 1.1, and exploratory objectives for immune-response RECIST criteria. Sample size increased to 180. Added an alternative Q2W dose-escalation schedule for dose-escalation phase. Defined 2 cohorts for the dose-expansion phase (treatment- naïve participants, and participants who received 1 or 2 prior lines of therapy). Expanded the rule for main Q4W Schedule dose-escalation and de-escalation for MEDI4736. Updated the escalation and de-escalation rules for Q2W cohorts. Clarified that the MTD will be determined for both dosing schedules (Q4W and Q2W). Added an alternative Q2W dose-escalation schedule. Added global lung cancer incidence data. Updated inclusion and exclusion criteria, medical history, smoking history, and physical examination text. Removed patient-reported outcomes. Updated the text related to participants with known central nervous system metastases. Updated the methods for assigning treatment groups, prohibited concomitant medications, and analysis text.
20 April 2015	Added the selected dose for the expansion phase. Added the immunotherapy pretreated cohort to the protocol because safety data are needed in immunotherapy pretreated participants. Added a monotherapy cross-over cohort for participants who experienced irAEs during combination to allow continued immunotherapy treatment. Updated Section “Benefit-risk Evaluation”. Added secondary objective and end point of safety for MEDI4736 monotherapy. Updated study enrollment. Added description of the dose-expansion dose and the co-administration group. Added Sections “Treatment Beyond Progression” and “Treatment of Subjects after an Immune-related Adverse Event”. Added MTD evaluation during dose-expansion phase. Modified the discussion related to handling the laboratory abnormalities. Updated sample size. Updated enrollment/screening, inclusion, exclusion, and study treatment discontinuation criteria. Updated Section “Follow-up Period for Q4W and Q2W Schedules”. Removed patient-reported outcomes. Updated prohibited concomitant medications. Added gastrointestinal disorders as AESIs.
25 September 2015	Updated the evaluation of clinical activity of the MEDI4736 and tremelimumab combination in PD-L1-negative and PD-L1-positive NSCLC participants. Inclusion of both PD-L1-positive and PD-L1-negative participants allowed the assessment activity of the MEDI4736 and tremelimumab combination in the overall population and that seek to determine response rate differences, if any, between the 2 participant subgroups. Updated the primary objectives in the dose-expansion phase to describe objectives separately by cohort. Clarified the secondary objectives to describe objectives separately by cohort. Added the primary endpoint for Cohort B. Clarified the first secondary endpoint for assessment of antitumor activity to describe endpoints by cohort. Updated enrollment criteria, number of participants, and treatment regimen for Cohort B in dose-expansion phase. Added treatment beyond progression statement. Updated sample size and number of centers. Updated enrollment/screening, and inclusion, exclusion criteria. Clarified the study assessments for dose expansion phase.

05 February 2016	Justification for conducting Cohort C. Updated sample size and number of centers. Updated enrollment/screening, inclusion, exclusion, and dose modification criteria; and follow-up assessments. Updated analaysis statements.
11 February 2016	Updated the tremelimumab clinical data to be consistent with the current tremelimumab Investigator's Brochure. Revised the toxicity management guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported