Clinical trial results:
A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059)

Summary

EudraCT number	2014-003574-16
Trial protocol	PT LT EE FR RO IT
Global end of trial date	23 July 2021

Results information

Result version number	v1 (current)
This version publication date	30 July 2022
First version publication date	30 July 2022

Trial information

Trial identification

Sponsor protocol code	3475-059

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02335411
WHO universal trial number (UTN)	-
Other trial identifiers	Merck: MK-3475-059

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.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	23 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2021
Global end of trial reached?	Yes
Global end of trial date	23 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study of pembrolizumab (MK-3475) for advanced gastric or gastroesophageal junction adenocarcinoma; pembrolizumab will be given as monotherapy to participants who have had previous treatment or who are treatment-naïve; pembrolizumab will also be evaluated as combination therapy with cisplatin and 5-Fluorouracil (5-FU) or (Japan only) capecitabine in treatment-naïve participants. The primary study hypothesis is that pembrolizumab will provide a clinically meaningful Overall Response Rate (ORR).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 12
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 45
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 139

Worldwide total number of subjects	315
EEA total number of subjects	44

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)	180
From 65 to 84 years	135
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female participants of at least 18 years of age with recurrent or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma were enrolled in this study.

Pre-assignment

Screening details:

318 participants were originally allocated to the study. No study information was collected from 3 participants, who were excluded from all analyses, including disposition.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Pembrolizumab monotherapy, previously treated

Arm description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 52 months. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with stable disease (SD) or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W)

Arm title	Cohort 2: Pembrolizumab combination therapy, treatment naive

Arm description:

Participants received pembrolizumab 200 mg IV each 3-week cycle (Q3W) for up to 40 months + cisplatin 80 mg/m^2 IV Q3W for up to 6 cycles + 5-Fluorouracil (5-FU) 800 mg/m^2 IV on Days 1-5 every 3 weeks or (Japan only) capecitabine 1000 mg/m^2 orally, twice per day (BID) on Days 1-14 of each 3-week cycle. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg IV on Day 1 of each 3-week cycle (Q3W)

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	PLATINOL®

Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

80 mg/m^2 IV Q3W for up to 6 cycles

Investigational medicinal product name	5-Fluorouracil (5-FU)
Investigational medicinal product code	
Other name	ADRUCIL®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg/m^2 IV on Days 1-5 every 3 weeks

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	XELODA®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Instead of 5-FU in Japan only: 1000 mg/m^2 orally, twice per day (BID) on Days 1-14 of each 3-week cycle

Arm title	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +

Arm description:

Programmed death-ligand 1 (PD-L1) positive participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 52 months. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	MK-3475
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg IV on Day 1 of each 3-week cycle (Q3W)

Number of subjects in period 1	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +
Started	259	25	31
Second Course Pembrolizumab	3	1	2
Completed	0	0	0
Not completed	259	25	31
Physician decision	3	-	-
Consent withdrawn by subject	11	-	3
Adverse event, non-fatal	9	-	-
Death	223	22	26

Sponsor Decision	12	3	2
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1: Pembrolizumab monotherapy, previously treated

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 52 months. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with stable disease (SD) or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Reporting group title	Cohort 2: Pembrolizumab combination therapy, treatment naive

Reporting group description:

Participants received pembrolizumab 200 mg IV each 3-week cycle (Q3W) for up to 40 months + cisplatin 80 mg/m^2 IV Q3W for up to 6 cycles + 5-Fluorouracil (5-FU) 800 mg/m^2 IV on Days 1-5 every 3 weeks or (Japan only) capecitabine 1000 mg/m^2 orally, twice per day (BID) on Days 1-14 of each 3-week cycle. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Reporting group title	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +

Reporting group description:

Programmed death-ligand 1 (PD-L1) positive participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 52 months. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Reporting group values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +
Number of subjects	259	25	31
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)	148	14	18
From 65-84 years	111	11	13
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	61.0	58.8	60.3
standard deviation	± 11.4	± 16.6	± 11.2
Sex: Female, Male Units: Participants			
Female	61	9	12
Male	198	16	19

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	41	17	15
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	0	0
White	200	8	16
More than one race	2	0	0
Unknown or Not Reported	11	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	17	1	3
Not Hispanic or Latino	228	23	28
Unknown or Not Reported	14	1	0

Reporting group values	Total		
Number of subjects	315		
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)	180		
From 65-84 years	135		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	82		
Male	233		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	73		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	5		
White	224		
More than one race	2		
Unknown or Not Reported	11		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	21		
Not Hispanic or Latino	279		

Unknown or Not Reported	15		

End points

End points reporting groups

Reporting group title	Cohort 1: Pembrolizumab monotherapy, previously treated

Reporting group description:

Participants received pembrolizumab 200 mg intravenously (IV) on Day 1 of each 3-week cycle (Q3W) for up to 52 months. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with stable disease (SD) or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Reporting group title	Cohort 2: Pembrolizumab combination therapy, treatment naive

Reporting group description:

Participants received pembrolizumab 200 mg IV each 3-week cycle (Q3W) for up to 40 months + cisplatin 80 mg/m^2 IV Q3W for up to 6 cycles + 5-Fluorouracil (5-FU) 800 mg/m^2 IV on Days 1-5 every 3 weeks or (Japan only) capecitabine 1000 mg/m^2 orally, twice per day (BID) on Days 1-14 of each 3-week cycle. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Reporting group title	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +

Reporting group description:

Programmed death-ligand 1 (PD-L1) positive participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 52 months. Eligible participants allocated to the pembrolizumab first course, who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg of each 3 week cycle for up to 17 cycles up to approximately an additional year.

Primary: Number of Participants Experiencing Adverse Events (AEs)

End point title	Number of Participants Experiencing Adverse Events (AEs)[1]

End point description:

An AE is defined as any untoward medical occurrence in a participant administered study drug and which does not necessarily have to have a causal relationship with the study drug. The number of participants who experienced at least one AE is presented. Per protocol, the number of participants who experienced at least one AE during first course pembrolizumab treatment is presented. The population analyzed was all enrolled participants who received ≥1 dose of study drug.

End point type	Primary

End point timeframe:

Up to approximately 65 months

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 comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259	25	31	
Units: Participants	248	25	31	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Discontinuing Study Drug Due to AEs

End point title	Number of Participants Discontinuing Study Drug Due to AEs[2]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered study drug and which does not necessarily have to have a causal relationship with the study drug. The number of participants who discontinued study drug due to an AE is presented. Per protocol, the number of participants who discontinued drug during first course pembrolizumab treatment is presented. The population analyzed was all enrolled participants who received ≥1 dose of study drug.

End point type	Primary

End point timeframe:

Up to approximately 52 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259	25	31	
Units: Participants	18	4	0	

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) For All Participants in Cohorts 1 and 3

End point title	Objective Response Rate (ORR) For All Participants in Cohorts 1 and 3[3]

End point description:

The Objective Response Rate (ORR) was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by central radiology review. The percentage of all participants (regardless of programmed death-ligand 1 [PD-L1] tumor status) in Cohorts 1 and 3 who had a CR or PR during first course pembrolizumab treatment per protocol, is presented. The population analyzed was all enrolled participants in Cohorts 1 and 3 who received ≥1 dose of study drug. Per protocol, Cohort 2 was not included in this outcome measure.

End point type	Primary

End point timeframe:

Up to approximately 75 months

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 comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259	0[4]	31	
Units: Percentage of Participants				
number (confidence interval 95%)	11.6 (8.0 to 16.1)	(to)	22.6 (9.6 to 41.1)	

Notes:

[4] - Per protocol, Cohort 2 was not included in this outcome measure.

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate For PD-L1 Positive Participants in Cohorts 1 and 3

End point title	Objective Response Rate For PD-L1 Positive Participants in Cohorts 1 and 3[5]

End point description:

The ORR was defined as the percentage of participants in the analysis population who had a CR or PR (CR: Disappearance of all target lesions; PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, as assessed by central radiology review. The percentage of all participants in Cohorts 1 and 3 with PD-L1+ tumor status who experienced a CR or PR during first course pembrolizumab treatment per protocol, is presented. Note: All participants in Cohort 3 had a PD-L1-positive tumor status. The population analyzed was all enrolled participants in Cohorts 1 and 3 with a positive PD-L1 tumor status who received ≥1 dose of study drug. Per protocol, Cohort 2 was not included in this outcome measure.

End point type	Primary

End point timeframe:

Up to approximately 75 months

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 comparisons between treatment groups were neither planned nor performed for this primary endpoint.

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	0[6]	31	
Units: Percentage of Participants				
number (confidence interval 95%)	15.5 (10.1 to 22.4)	(to)	22.6 (9.6 to 41.1)	

Notes:

[6] - Per protocol, Cohort 2 was not included in this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) For All Participants in Cohort 2

End point title	Objective Response Rate (ORR) For All Participants in Cohort 2

End point description:

The Objective Response Rate (ORR) was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by central radiology review. The percentage of all participants (regardless of PD-L1 tumor status) in Cohort 2 who had a CR or PR during first course pembrolizumab treatment per protocol, is presented. The population analyzed was all enrolled participants in Cohort 2 who received ≥1 dose of study drug. Per protocol, Cohorts 1 and 3 were not included in this outcome measure.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	25	0[8]	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	60.0 (38.7 to 78.9)	(to)	

Notes:

[7] - Per protocol, Cohort 1 was not included in this outcome measure.

[8] - Per protocol, Cohort 3 was not included in this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate For PD-L1 Positive Participants in Cohort 2

End point title	Objective Response Rate For PD-L1 Positive Participants in Cohort 2

End point description:

The ORR was defined as the percentage of participants in the analysis population who had a CR or PR (CR: Disappearance of all target lesions; PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, as assessed by central radiology review. The percentage of participants in Cohort 2 with PD-L1+ tumor status who experienced a CR or PR during first course pembrolizumab treatment per protocol, is presented. The population analyzed was all enrolled participants in Cohort 2 with a positive PD-L1 tumor status who received ≥1 dose of study drug. Per protocol, Cohorts 1 and 3

were not included in this outcome measure.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[9]	15	0[10]	
Units: Percentage of Participants				
number (confidence interval 95%)	(to)	73.3 (44.9 to 92.2)	(to)	

Notes:

[9] - Per protocol, Cohort 1 was not included in this outcome measure.

[10] - Per protocol, Cohort 3 was not included in this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) For All Participants

End point title	Duration of Response (DOR) For All Participants

End point description:

Duration of Response (DOR) was defined as the time from first documented evidence of CR or PR (CR: Disappearance of all target lesions; PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, based on central imaging vendor assessment, until disease progression (PD) or death, whichever occurred first. PD is defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions is also considered PD. Participants who had not progressed or died at the time of analysis were censored at the date of their last tumor assessment. The DOR for all participants (regardless of PD-L1 tumor status) during first course pembrolizumab treatment per protocol, is presented. The population analyzed was all enrolled participants who received ≥1 dose of study drug and demonstrated a confirmed response (CR or PR).

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30[11]	15[12]	7[13]	
Units: Months				
median (full range (min-max))	16.1 (2.4 to 99999)	4.6 (2.6 to 99999)	38.0 (2.1 to 99999)	

Notes:

[11] - 99999=Upper limit not reached due to insufficient number of responders with relapse.

[12] - 99999=Upper limit not reached due to insufficient number of responders with relapse.

[13] - 99999=Upper limit not reached due to insufficient number of responders with relapse.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response For PD-L1 Positive Participants

End point title	Duration of Response For PD-L1 Positive Participants

End point description:

DOR was defined as the time from first documented evidence of CR or PR (CR: Disappearance of all target lesions; PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1, based on central imaging vendor assessment, until disease progression (PD) or death, whichever occurred first. PD is ≥20% increase in the sum of diameters of target lesions; the sum must also increase by ≥5 mm. The appearance of one or more new lesions is also considered PD. Participants who had not progressed or died at the time of analysis were censored at the date of their last tumor assessment. The DOR for only PD-L1 positive participants during first course pembrolizumab treatment per protocol, is presented. Note: All participants in Cohort 3 had a PD-L1-positive tumor status. The population analyzed was all enrolled participants with a positive PD-L1 tumor status who received ≥1 dose of study drug and demonstrated a confirmed response (CR or PR).

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23[14]	11[15]	7[16]	
Units: Months				
median (full range (min-max))	99999 (99999 to 99999)	4.6 (3.2 to 99999)	38.0 (2.1 to 99999)	

Notes:

[14] - 99999=Median, upper, lower limits not reached due to insufficient number of responders with relapse.

[15] - 99999=Upper limit not reached due to insufficient number of responders with relapse.

[16] - 99999=Upper limit not reached due to insufficient number of responders with relapse.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) For All Participants

End point title	Progression-Free Survival (PFS) For All Participants

End point description:

Progression-Free Survival (PFS) was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions, taking as

reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. The PFS for all participants (regardless of PD-L1 tumor status) during first course pembrolizumab treatment per protocol, is presented. The population analyzed was all enrolled participants who received ≥1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259	25	31	
Units: Months				
median (confidence interval 95%)	2.0 (2.0 to 2.0)	6.6 (5.9 to 10.6)	2.9 (2.0 to 6.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival For PD-L1 Positive Participants

End point title	Progression-Free Survival For PD-L1 Positive Participants

End point description:

PFS was defined as the time from randomization to the first documented disease progression, or death due to any cause, whichever occurred first. Per RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered progression. The PFS for only PD-L1 positive participants during first course pembrolizumab treatment per protocol, is presented. Note: All participants in Cohort 3 had a PD-L1-positive tumor status. The population analyzed was all enrolled participants with a positive PD-L1 tumor status who received ≥1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	15	31	
Units: Months				
median (confidence interval 95%)	2.1 (2.0 to 2.1)	6.5 (4.7 to 7.9)	2.9 (2.0 to 6.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) For All Participants

End point title	Overall Survival (OS) For All Participants

End point description:

Overall Survival (OS) was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. The OS for all participants (regardless of PD-L1 tumor status) during first course pembrolizumab treatment per protocol, is presented. The population analyzed was all enrolled participants who received ≥1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259	25	31	
Units: Months				
median (confidence interval 95%)	5.5 (4.2 to 6.7)	13.8 (8.6 to 25.6)	20.7 (10.0 to 29.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival For PD-L1 Positive Participants

End point title	Overall Survival For PD-L1 Positive Participants

End point description:

OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the final analysis were censored at the date of the last follow-up. The OS for only PD-L1 positive participants during first course pembrolizumab treatment per protocol, is presented. Note: All participants in Cohort 3 had a PD-L1-positive tumor status. The population analyzed was all enrolled participants with a positive PD-L1 tumor status who received ≥1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	15	31	
Units: Months				
median (confidence interval 95%)	5.8 (4.4 to 7.8)	11.1 (5.4 to 22.3)	20.7 (10.0 to 29.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) For All Participants

End point title	Disease Control Rate (DCR) For All Participants

End point description:

Disease Control Rate (DCR) was defined as the percentage of participants in the analysis population who had a CR or a PR (CR: Disappearance of all target lesions; PR: At least a 30% decrease in the sum of diameters of target lesions) or stable disease (SD); (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease) for ≥6 months, (for Cohort 1 ≥2 months) as assessed by central radiology review. The percentage of all participants (regardless of PD-L1 tumor status) who had a CR or PR or SD during first course pembrolizumab treatment per protocol, is presented. The population analyzed was all enrolled participants who received ≥1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	259	25	31	
Units: Percentage of Participants				
number (confidence interval 95%)	27.0 (21.7 to 32.9)	80.0 (59.3 to 93.2)	32.3 (16.7 to 51.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate For PD-L1 Positive Participants

End point title	Disease Control Rate For PD-L1 Positive Participants

End point description:

DCR was defined as the percentage of participants in the analysis population who had a CR or a PR (CR: Disappearance of all target lesions; PR: At least a 30% decrease in the sum of diameters of target lesions) or stable disease (SD); (SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease) for ≥6 months, (for Cohort 1 ≥2 months) as assessed by central radiology review. The percentage of participants with PD-L1+ tumor status who experienced a CR or PR or SD during first course pembrolizumab treatment per protocol, is presented. Note: All participants in Cohort 3 had a PD-L1-positive tumor status. The population analyzed was all enrolled participants with a positive PD-L1 tumor status who received ≥1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to approximately 75 months

End point values	Cohort 1: Pembrolizumab monotherapy, previously treated	Cohort 2: Pembrolizumab combination therapy, treatment naive	Cohort 3: Pembrolizumab monotherapy, treatment naive, PD-L1 +	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	15	31	
Units: Percentage of Participants				
number (confidence interval 95%)	33.1 (25.6 to 41.3)	80.0 (51.9 to 95.7)	32.3 (16.7 to 51.4)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 75 months

Adverse event reporting additional description:

The all-cause mortality population consisted of all allocated participants. The population for AEs consisted of all allocated participants who received ≥1 dose of study drug. The following AE preferred terms not related to the drug were excluded: Neoplasm progression, Malignant neoplasm progression and Disease progression.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Cohort 1 First Course

Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 52 months.

Reporting group title	Cohort 2 First Course

Reporting group description:

Participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 40 months + cisplatin 80 mg/m^2 IV Q3W for up to 6 cycles + 5-FU 800 mg/m^2 IV on Days 1-5 every 3 weeks or (Japan only) capecitabine 1000 mg/m^2 orally, BID on Days 1-14 of each 3-week cycle.

Reporting group title	Cohort 2 Second Course

Reporting group description:

Eligible participants allocated to the pembrolizumab first course in Cohort 2 who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg on Day 1 of each 3 week cycle (Q3W) for up to 17 cycles up to approximately an additional year.

Reporting group title	Cohort 1 Second Course

Reporting group description:

Eligible participants allocated to the pembrolizumab first course in Cohort 1 who stopped pembrolizumab with stable disease (SD) or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg on Day 1 of each 3 week cycle (Q3W) for up to 17 cycles up to approximately an additional year.

Reporting group title	Cohort 3 Second Course

Reporting group description:

Eligible participants allocated to the pembrolizumab first course in Cohort 3 who stopped pembrolizumab with SD or better, initiated a second course of pembrolizumab at the investigator's discretion at 200 mg on Day 1 of each 3 week cycle (Q3W) for up to 17 cycles up to approximately an additional year.

Reporting group title	Cohort 3 First Course

Reporting group description:

PD-L1 positive participants received pembrolizumab 200 mg IV on Day 1 of each 3-week cycle (Q3W) for up to 52 months.

Serious adverse events	Cohort 1 First Course	Cohort 2 First Course	Cohort 2 Second Course
Total subjects affected by serious adverse events			
subjects affected / exposed	119 / 259 (45.95%)	11 / 25 (44.00%)	0 / 1 (0.00%)
number of deaths (all causes)	244	21	1
number of deaths resulting from adverse events	2	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Metastases to adrenals			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (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
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			

subjects affected / exposed	1 / 259 (0.39%)	1 / 25 (4.00%)	0 / 1 (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
Haematoma			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 259 (1.54%)	0 / 25 (0.00%)	0 / 1 (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
Chest pain			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (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
Death			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Fatigue			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal complication associated with device			

subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Influenza like illness			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (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 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 259 (1.16%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (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
Hypoxia			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Pleural effusion			

subjects affected / exposed	9 / 259 (3.47%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	2 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Pulmonary embolism			
subjects affected / exposed	6 / 259 (2.32%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Confusional state			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Delirium			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Depression			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Drug dependence			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (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	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (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 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Blood bilirubin increased			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Urine output decreased			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Injury, poisoning and procedural complications			
Anastomotic stenosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Rib fracture			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Thoracic vertebral fracture			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (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
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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			
Atrial fibrillation			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Myocardial infarction			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Pericardial effusion			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Supraventricular tachycardia			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Cauda equina syndrome			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Dizziness			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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	1 / 259 (0.39%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Unresponsive to stimuli			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Vertebral artery occlusion			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Anaemia			
subjects affected / exposed	6 / 259 (2.32%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diffuse uveal melanocytic proliferation			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 259 (1.54%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (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
Ascites			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Colitis			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Constipation			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (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

Diarrhoea			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (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
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Dysphagia			
subjects affected / exposed	7 / 259 (2.70%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric stenosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haematemesis			

subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Ileus			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Intestinal obstruction			
subjects affected / exposed	6 / 259 (2.32%)	0 / 25 (0.00%)	0 / 1 (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
Jejunal perforation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Large intestinal obstruction			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Melaena			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Nausea			
subjects affected / exposed	5 / 259 (1.93%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	3 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Oesophageal intramural haematoma			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Oesophageal perforation			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Oesophageal stenosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Oesophageal ulcer			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Stomatitis			
subjects affected / exposed	0 / 259 (0.00%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	5 / 259 (1.93%)	0 / 25 (0.00%)	0 / 1 (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
Hepatobiliary disorders			
Bile duct stenosis			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Biliary obstruction			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Cholecystitis acute			
subjects affected / exposed	1 / 259 (0.39%)	1 / 25 (4.00%)	0 / 1 (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
Hepatic failure			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Hepatic function abnormal			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Hepatic haematoma			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Hepatic pain			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Hepatitis			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Jaundice			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Portal vein thrombosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Skin and subcutaneous tissue disorders			
Lichen planus			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Rash maculo-papular			
subjects affected / exposed	0 / 259 (0.00%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 259 (2.32%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	3 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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

Hydronephrosis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Nephrotic syndrome			
subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Thyroiditis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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
Back pain			
subjects affected / exposed	5 / 259 (1.93%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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

Myositis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Neck pain			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Pain in extremity			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (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
Polymyalgia rheumatica			
subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Bacteraemia			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Disseminated varicella zoster virus infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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

Diverticulitis intestinal haemorrhagic			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Encephalitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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 abscess			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Osteomyelitis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Pharyngitis			
subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 259 (0.00%)	1 / 25 (4.00%)	0 / 1 (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
Pneumonia			
subjects affected / exposed	4 / 259 (1.54%)	0 / 25 (0.00%)	0 / 1 (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
Pyelonephritis			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Sepsis			

subjects affected / exposed	5 / 259 (1.93%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Subdiaphragmatic abscess			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Urinary tract infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 259 (0.39%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 259 (1.54%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			

subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Hypercalcaemia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Hyperglycaemia			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (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
Hyponatraemia			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (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

Serious adverse events	Cohort 1 Second Course	Cohort 3 Second Course	Cohort 3 First Course
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	15 / 31 (48.39%)
number of deaths (all causes)	1	1	26
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Metastases to adrenals			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal squamous cell carcinoma			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 cancer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Vena cava thrombosis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 complication associated with device			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 like illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Non-cardiac chest pain			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Confusional state			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Delirium			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Depression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug dependence			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
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 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Urine output decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			
Anastomotic stenosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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

Rib fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 pseudoaneurysm			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			
Atrial fibrillation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			
Altered state of consciousness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Cauda equina syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Unresponsive to stimuli			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Vertebral artery occlusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Eye disorders			
Diffuse uveal melanocytic proliferation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Ascites			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Colitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Gastric haemorrhage			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Gastric perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Gastric stenosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Haematemesis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Intestinal obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Jejunal perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 intestinal obstruction			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Melaena			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Obstruction gastric			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Oesophageal intramural haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Oesophageal perforation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Oesophageal stenosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Oesophageal ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Biliary obstruction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 haematoma			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Jaundice			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Portal vein thrombosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			
Lichen planus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic kidney disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Hydronephrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Nephrotic syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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			

Abdominal abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Disseminated varicella zoster virus infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 intestinal haemorrhagic			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Encephalitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Liver abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Osteomyelitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Pharyngitis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Septic shock			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Wound infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (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

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

Non-serious adverse events	Cohort 1 First Course	Cohort 2 First Course	Cohort 2 Second Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	237 / 259 (91.51%)	25 / 25 (100.00%)	0 / 1 (0.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 259 (5.41%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	20	1	0
Hypotension			
subjects affected / exposed	10 / 259 (3.86%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	12	0	0
Vasculitis			
subjects affected / exposed	0 / 259 (0.00%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	24 / 259 (9.27%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	26	7	0
Chest discomfort			
subjects affected / exposed	2 / 259 (0.77%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	93 / 259 (35.91%)	10 / 25 (40.00%)	0 / 1 (0.00%)
occurrences (all)	105	13	0
Generalised oedema			
subjects affected / exposed	0 / 259 (0.00%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	4 / 259 (1.54%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	5	0	0
Malaise			
subjects affected / exposed	7 / 259 (2.70%)	5 / 25 (20.00%)	0 / 1 (0.00%)
occurrences (all)	7	14	0
Mucosal inflammation			

subjects affected / exposed	1 / 259 (0.39%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
Oedema			
subjects affected / exposed	9 / 259 (3.47%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	9	10	0
Oedema peripheral			
subjects affected / exposed	43 / 259 (16.60%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	57	1	0
Pyrexia			
subjects affected / exposed	25 / 259 (9.65%)	6 / 25 (24.00%)	0 / 1 (0.00%)
occurrences (all)	35	9	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	44 / 259 (16.99%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	50	2	0
Dyspnoea			
subjects affected / exposed	40 / 259 (15.44%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	43	2	0
Epistaxis			
subjects affected / exposed	3 / 259 (1.16%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	3	2	0
Hiccups			
subjects affected / exposed	4 / 259 (1.54%)	8 / 25 (32.00%)	0 / 1 (0.00%)
occurrences (all)	4	16	0
Oropharyngeal pain			
subjects affected / exposed	8 / 259 (3.09%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	8	2	0
Pleural effusion			
subjects affected / exposed	11 / 259 (4.25%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	14	2	0
Pneumonitis			
subjects affected / exposed	2 / 259 (0.77%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	15 / 259 (5.79%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	18	0	0
Insomnia			
subjects affected / exposed	17 / 259 (6.56%)	9 / 25 (36.00%)	0 / 1 (0.00%)
occurrences (all)	20	9	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	14 / 259 (5.41%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	19	3	0
Aspartate aminotransferase increased			
subjects affected / exposed	30 / 259 (11.58%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	34	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	31 / 259 (11.97%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	32	1	0
Blood creatinine increased			
subjects affected / exposed	13 / 259 (5.02%)	5 / 25 (20.00%)	0 / 1 (0.00%)
occurrences (all)	15	6	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 259 (2.70%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	9	2	0
Haemoglobin decreased			
subjects affected / exposed	4 / 259 (1.54%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
Lymphocyte count decreased			
subjects affected / exposed	6 / 259 (2.32%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	8	0	0
Neutrophil count decreased			
subjects affected / exposed	2 / 259 (0.77%)	13 / 25 (52.00%)	0 / 1 (0.00%)
occurrences (all)	3	30	0
Platelet count decreased			
subjects affected / exposed	3 / 259 (1.16%)	5 / 25 (20.00%)	0 / 1 (0.00%)
occurrences (all)	4	7	0
Weight decreased			

subjects affected / exposed	38 / 259 (14.67%)	5 / 25 (20.00%)	0 / 1 (0.00%)
occurrences (all)	41	6	0
Weight increased			
subjects affected / exposed	2 / 259 (0.77%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	2	13	0
White blood cell count decreased			
subjects affected / exposed	2 / 259 (0.77%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	2	9	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	17 / 259 (6.56%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	17	5	0
Dysgeusia			
subjects affected / exposed	6 / 259 (2.32%)	6 / 25 (24.00%)	0 / 1 (0.00%)
occurrences (all)	6	9	0
Headache			
subjects affected / exposed	12 / 259 (4.63%)	5 / 25 (20.00%)	0 / 1 (0.00%)
occurrences (all)	13	5	0
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 259 (1.93%)	6 / 25 (24.00%)	0 / 1 (0.00%)
occurrences (all)	5	7	0
Neuropathy peripheral			
subjects affected / exposed	3 / 259 (1.16%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	3	3	0
Syncope			
subjects affected / exposed	2 / 259 (0.77%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	3	3	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	58 / 259 (22.39%)	11 / 25 (44.00%)	0 / 1 (0.00%)
occurrences (all)	69	13	0
Leukopenia			
subjects affected / exposed	4 / 259 (1.54%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	7	3	0
Neutropenia			

subjects affected / exposed	3 / 259 (1.16%)	9 / 25 (36.00%)	0 / 1 (0.00%)
occurrences (all)	3	12	0
Thrombocytopenia			
subjects affected / exposed	8 / 259 (3.09%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	10	5	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 259 (0.00%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	0	4	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 259 (0.77%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	2	2	0
Abdominal distension			
subjects affected / exposed	15 / 259 (5.79%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	15	2	0
Abdominal pain			
subjects affected / exposed	49 / 259 (18.92%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	56	3	0
Abdominal pain upper			
subjects affected / exposed	19 / 259 (7.34%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	25	8	0
Ascites			
subjects affected / exposed	16 / 259 (6.18%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	18	0	0
Constipation			
subjects affected / exposed	52 / 259 (20.08%)	14 / 25 (56.00%)	0 / 1 (0.00%)
occurrences (all)	57	22	0
Diarrhoea			
subjects affected / exposed	46 / 259 (17.76%)	14 / 25 (56.00%)	0 / 1 (0.00%)
occurrences (all)	55	18	0
Dry mouth			
subjects affected / exposed	8 / 259 (3.09%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	8	4	0
Dyspepsia			

subjects affected / exposed	9 / 259 (3.47%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	9	3	0
Dysphagia			
subjects affected / exposed	31 / 259 (11.97%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	36	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	10 / 259 (3.86%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	12	4	0
Nausea			
subjects affected / exposed	65 / 259 (25.10%)	15 / 25 (60.00%)	0 / 1 (0.00%)
occurrences (all)	74	22	0
Stomatitis			
subjects affected / exposed	10 / 259 (3.86%)	17 / 25 (68.00%)	0 / 1 (0.00%)
occurrences (all)	10	29	0
Vomiting			
subjects affected / exposed	36 / 259 (13.90%)	10 / 25 (40.00%)	0 / 1 (0.00%)
occurrences (all)	44	23	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 259 (1.16%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	3	4	0
Dry skin			
subjects affected / exposed	17 / 259 (6.56%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	18	2	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 259 (0.39%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	1	3	0
Pruritus			
subjects affected / exposed	33 / 259 (12.74%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	39	7	0
Rash			
subjects affected / exposed	31 / 259 (11.97%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	33	2	0
Rash maculo-papular			

subjects affected / exposed	5 / 259 (1.93%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	5	1	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 259 (0.39%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	1	2	0
Skin lesion			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Urticaria			
subjects affected / exposed	1 / 259 (0.39%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	10 / 259 (3.86%)	4 / 25 (16.00%)	0 / 1 (0.00%)
occurrences (all)	10	4	0
Hypothyroidism			
subjects affected / exposed	24 / 259 (9.27%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	24	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 259 (13.90%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	58	3	0
Back pain			
subjects affected / exposed	34 / 259 (13.13%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	38	2	0
Flank pain			
subjects affected / exposed	5 / 259 (1.93%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	5	0	0
Groin pain			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Muscular weakness			
subjects affected / exposed	3 / 259 (1.16%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	3	0	0
Myalgia			

subjects affected / exposed	8 / 259 (3.09%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	10	2	0
Pain in extremity			
subjects affected / exposed	9 / 259 (3.47%)	0 / 25 (0.00%)	0 / 1 (0.00%)
occurrences (all)	12	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 259 (2.70%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	8	2	0
Pneumonia			
subjects affected / exposed	8 / 259 (3.09%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	10	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	73 / 259 (28.19%)	13 / 25 (52.00%)	0 / 1 (0.00%)
occurrences (all)	81	22	0
Dehydration			
subjects affected / exposed	15 / 259 (5.79%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	20	2	0
Diabetes mellitus			
subjects affected / exposed	0 / 259 (0.00%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			
subjects affected / exposed	23 / 259 (8.88%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	29	6	0
Hypoalbuminaemia			
subjects affected / exposed	24 / 259 (9.27%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	24	1	0
Hypokalaemia			
subjects affected / exposed	12 / 259 (4.63%)	3 / 25 (12.00%)	0 / 1 (0.00%)
occurrences (all)	13	3	0
Hypomagnesaemia			
subjects affected / exposed	2 / 259 (0.77%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	2	2	0
Hyponatraemia			

subjects affected / exposed	23 / 259 (8.88%)	1 / 25 (4.00%)	0 / 1 (0.00%)
occurrences (all)	26	2	0
Hypophosphataemia			
subjects affected / exposed	10 / 259 (3.86%)	2 / 25 (8.00%)	0 / 1 (0.00%)
occurrences (all)	14	4	0

Non-serious adverse events	Cohort 1 Second Course	Cohort 3 Second Course	Cohort 3 First Course
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	31 / 31 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Vasculitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Chest discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	10 / 31 (32.26%)
occurrences (all)	0	0	10
Generalised oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	5
Malaise			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	6
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	6 / 31 (19.35%)
occurrences (all)	0	0	8
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	5 / 31 (16.13%)
occurrences (all)	0	0	7
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Pneumonitis			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	6
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Lymphocyte count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Neutrophil count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	6
Platelet count decreased			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	4
Weight increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	6
Dysgeusia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	6
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	7 / 31 (22.58%)
occurrences (all)	0	0	9
Leukopenia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	8 / 31 (25.81%)
occurrences (all)	0	0	13
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Ascites			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	7 / 31 (22.58%)
occurrences (all)	0	0	7
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	8 / 31 (25.81%)
occurrences (all)	0	0	13
Dry mouth			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	4
Dysphagia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	8 / 31 (25.81%)
occurrences (all)	0	0	10
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	6 / 31 (19.35%)
occurrences (all)	0	0	12
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Dry skin			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	8 / 31 (25.81%)
occurrences (all)	0	0	10
Rash			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Rash maculo-papular			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
Skin hyperpigmentation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Hypothyroidism			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	5 / 31 (16.13%)
occurrences (all)	0	0	8
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	6 / 31 (19.35%)
occurrences (all)	0	0	7
Flank pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Muscular weakness			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	5 / 31 (16.13%)
occurrences (all)	0	0	7
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	5 / 31 (16.13%)
occurrences (all)	0	0	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	11 / 31 (35.48%)
occurrences (all)	0	0	14
Dehydration			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	4
Diabetes mellitus			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	4
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			

subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 2 (0.00%)	0 / 31 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2015	Amendment 01: Corrected exclusion criterion no. 2 (participant will be excluded if he/she has active autoimmune disease).
22 June 2015	Amendment 04: Removed the Myeloid-Derived Suppressor Cells (MDSC) biomarker endpoint and electronic patient reported outcome (ePRO) procedures, reduced sample size for Cohorts 2 and 3, clarified the dose regiment for 5-FU (fixed at continuous 120-hour IV infusion) and allowed the substitution of 5-FU for capecitabine for participants in Japan only.
23 February 2016	Amendment 02: Added language to further define appropriate tumor sampling for the trial and incorporated investigational new drug (IND) review period.
13 December 2016	Amendment 07: Modified protocol language to the outcome of the interim analysis of Cohort 1, increased the sample size in Cohort 1, modified primary efficacy objective for Cohort 1 to indicate that estimation will be utilized and changed participant inclusion/exclusion criteria as recommended by the external scientific advisory committee (SAC) to ensure entry of participants with the ability to participate for the full duration of the trial.
13 December 2016	Amendment 09: Included additional language on discontinuation due to recurrent Grade 2 pneumonitis regarding dose modification to be consistent with the overall pembrolizumab program.
19 December 2017	Amendment 10: Added language to the Dose Modification for Pembrolizumab Table to clarify the guidance and management of myocarditis. - To enable survival follow-up activities; Removed Anti-Drug Antibodies (ADA) and Pharmacokinetic (PK) sample collection. - To Table 7, the reference to the Events of Clinical Interest (ECI) guidance document was removed
20 October 2020	Amendment 12: Added language to allow participants to rollover to an extension study. Removed cohort 4 from Amendment 11 which was never implemented at sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Per protocol, response/progression or adverse events during the second pembrolizumab course were not counted towards efficacy outcome measures or safety outcome measures respectively.

Notes: