Clinical trial results:
A Phase II Multi-Center Study of BGB324 in Combination with Pembrolizumab in Patients with Previously Treated Advanced Adenocarcinoma of the Lung

Summary

EudraCT number	2016-003609-32
Trial protocol	NO GB ES
Global end of trial date	27 October 2022

Results information

Result version number	v1 (current)
This version publication date	15 November 2023
First version publication date	15 November 2023

Trial information

Trial identification

Sponsor protocol code	BGBC008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03184571
WHO universal trial number (UTN)	-
Other trial identifiers	MSD: MK-3475 PN531

Notes:

Sponsors

Sponsor organisation name	BerGenBio ASA
Sponsor organisation address	Mollendalsbakken 9, Bergen, Norway, 5009
Public contact	Clinical Project Manager, BerGenBio ASA, +47 55961159, regulatory.bgbc008@bergenbio.com
Scientific contact	Clinical Project Manager, BerGenBio ASA, +47 55961159, regulatory.bgbc008@bergenbio.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	20 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the anti-tumor activity of bemcentinib and pembrolizumab when given in combination.

Protection of trial subjects:

The study was conducted in accordance with International Council for Harmonization , Good clinical practice (GCP), the Declaration of Helsinki, the European Union Clinical Trials Directive 2001/20/EC, the GCP Directive 2005/28/EC, the requirements of local , Institutional Ethics Committee/ Institutional Review Board and the United States (US) Code of Federal Regulations (CFR), Title 21 CFR Part 50.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 10
Country: Number of subjects enrolled	Spain: 64
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	99
EEA total number of subjects	74

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)	46
From 65 to 84 years	52

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 138 subjects were enrolled in study, of these 39 subjects did not receive any treatment for the following reasons: 30 screen failures; 2 due to death; 2 due to voluntary withdrawal; 2 lost to follow-up and 3 due to an unspecified reason.

Pre-assignment

Screening details:

A total of 138 subjects were enrolled in the study, however, the subject information detailed in this record relates to the 99 subjects who received at least one dose of study treatment (bemcentinib and pembrolizumab).

Period 1

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

Blinding implementation details:

This was an open label study, no randomization and blinding were used in this study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

This arm included subjects who had a maximum of one prior line of platinum-containing chemotherapy and had not received prior immunotherapy of any kind. During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.

Arm type	Experimental
Investigational medicinal product name	Bemcentinib
Investigational medicinal product code	BGB324
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Bemcentinib was administered as follows: a loading dose of 400 milligrams (mg) was administered on Days 1, 2, and 3, followed by a daily dose of 200 mg from Day 4 onwards.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	Keytruda
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 200 mg pembrolizumab was given to subjects by intravenous (IV) infusion over 30 minutes every 3 weeks.

Arm title	Cohort B

Arm description:

This arm included subjects who had a maximum of one prior line of an anti-PD-(L)1 therapy (monotherapy). During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.

Arm type	Experimental

Investigational medicinal product name	Bemcentinib
Investigational medicinal product code	BGB324
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Bemcentinib was administered as follows: a loading dose of 400 mg was administered on Days 1, 2, and 3, followed by a daily dose of 200 mg from Day 4 onwards.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	Keytruda
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 200 mg pembrolizumab was given to subjects by IV infusion over 30 minutes every 3 weeks.

Arm title	Cohort C

Arm description:

This arm included subjects who had a maximum of one prior line of therapy with an anti-PD-(L)1 therapy in combination with a platinum-containing chemotherapy. During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.

Arm type	Experimental
Investigational medicinal product name	Bemcentinib
Investigational medicinal product code	BGB324
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Bemcentinib was administered as follows: a loading dose of 400 mg was administered on Days 1, 2, and 3, followed by a daily dose of 200 mg from Day 4 onwards.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	Keytruda
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 200 mg pembrolizumab was given to subjects by IV infusion over 30 minutes every 3 weeks.

Number of subjects in period 1	Cohort A	Cohort B	Cohort C
Started	50	29	20
Completed	0	0	0
Not completed	50	29	20
Consent withdrawn by subject	2	-	-
Death	41	22	14
Unknown	6	7	6
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description:	
This arm included subjects who had a maximum of one prior line of platinum-containing chemotherapy and had not received prior immunotherapy of any kind. During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.	
Reporting group title	Cohort B
Reporting group description:	
This arm included subjects who had a maximum of one prior line of an anti-PD-(L)1 therapy (monotherapy). During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.	
Reporting group title	Cohort C
Reporting group description:	
This arm included subjects who had a maximum of one prior line of therapy with an anti-PD-(L)1 therapy in combination with a platinum-containing chemotherapy. During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.	

Reporting group values	Cohort A	Cohort B	Cohort C
Number of subjects	50	29	20
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)	23	13	10
From 65-84 years	27	15	10
85 years and over	0	1	0
Age continuous Units: years			
arithmetic mean	64.0	64.6	64.8
standard deviation	± 9.27	± 9.41	± 9.33
Gender categorical Units: Subjects			
Female	20	8	6
Male	30	21	14
Ethnicity Units: Subjects			
Hispanic or Latino	2	0	2
Not Hispanic or Latino	48	29	18
Race Units: Subjects			
White	47	27	20
Asian	2	0	0
Black	0	2	0

Other	1	0	0

Reporting group values	Total		
Number of subjects	99		
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)	46		
From 65-84 years	52		
85 years and over	1		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	34		
Male	65		
Ethnicity Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	95		
Race Units: Subjects			
White	94		
Asian	2		
Black	2		
Other	1		

End points

End points reporting groups

Reporting group title	Cohort A

Reporting group description:

This arm included subjects who had a maximum of one prior line of platinum-containing chemotherapy and had not received prior immunotherapy of any kind. During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.

Reporting group title	Cohort B

Reporting group description:

This arm included subjects who had a maximum of one prior line of an anti-PD-(L)1 therapy (monotherapy). During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.

Reporting group title	Cohort C

Reporting group description:

This arm included subjects who had a maximum of one prior line of therapy with an anti-PD-(L)1 therapy in combination with a platinum-containing chemotherapy. During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.

Primary: Percentage of Subjects with Objective Response Rate (ORR)

End point title	Percentage of Subjects with Objective Response Rate (ORR)[1]

End point description:

The ORR was defined as the percentage of evaluable subjects who had at least one (confirmed) overall response of complete response (CR) or partial response (PR) (defined by modified response evaluation criteria in solid tumors [RECIST] 1.1). The CR was defined as the disappearance of all target lesions (TLs) since baseline. Any pathological lymph nodes selected as TLs must have a reduction in the short axis to <10 millimeter (mm). And the PR was defined as at least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters. The Evaluable analysis set included all evaluable for efficacy subjects (EE), subjects that: (i) received at least one dose of pembrolizumab and bemcentinib, (ii) had measurable disease at study entry, as determined by the Investigator Site assessment, (iii) met the inclusion/exclusion criteria, and (iv) had at least one on-treatment scan.

End point type	Primary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

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: No hypothesis was tested using statistical analysis.

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	27	19	
Units: Percentage of subjects				
number (confidence interval 90%)	22.7 (12.9 to 35.5)	0 (0 to 10.5)	0 (0 to 14.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The DCR was defined as the percentage of evaluable subjects with a confirmed CR, confirmed PR, or stable disease (out of number evaluable subjects evaluable) (defined by modified RECIST 1.1). The CR was defined as the disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in the short axis to <10 mm. The PR was defined as at least a 30% decrease in the sum of the diameters of TLs, taking as reference the baseline sum of diameters. And SD Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progression of disease. The EE population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	27	19	
Units: Percentage of subjects				
number (confidence interval 95%)	54.5 (38.8 to 69.6)	44.4 (25.5 to 64.7)	52.6 (28.9 to 75.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Were Progression Free at 12 Months

End point title	Percentage of Subjects Who Were Progression Free at 12 Months

End point description:

The progression free survival (PFS) was defined as the time from start of treatment until the date of radiological disease progression (the date on which the confirmed progression was initially observed) or the date of death (whichever was earlier). Kaplan-Meier technique was used for calculation. The EE population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Up to 12 months following treatment initiation

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	27	19	
Units: Percentage of subjects				
number (confidence interval 95%)	43.2 (28.4 to 57.1)	16.7 (5.4 to 33.3)	31.6 (12.9 to 52.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Response (DoR)

End point title	Median Duration of Response (DoR)

End point description:

The DoR was defined as the time from the date of first documented response until the date of documented progression or death (in the absence of disease progression). The DoR was calculated only for the subjects who had an objective response. Kaplan-Meier technique was used for calculation. In data table below, "00000" suggests that median and 95% confidence interval (CI) was not estimable for cohorts B and C. In both cohorts no subject had a confirmed objective response, required for DOR analysis. The EE population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	27	19	
Units: Months				
median (confidence interval 95%)	8.1 (3.9 to 25.6)	00000 (00000 to 00000)	00000 (00000 to 00000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clinically Significant Laboratory Abnormalities

End point title	Number of Subjects With Clinically Significant Laboratory Abnormalities

End point description:

The number of subjects with clinically significant laboratory abnormality was assessed by physician, and were reported here. Laboratory tests included clinical chemistry, hematology, coagulation, and urinalysis. The safety set included all subjects who were enrolled in the study and were evaluable for safety (ES); subjects who received at least one dose of study treatment (bemcentinib and pembrolizumab). In below results: AST =aspartate aminotransferase, ALT = alanine aminotransferase, and GGT= Gamma-glutamyl transferase.

End point type	Secondary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Subjects				
Platelet count decreased (Hematology)	2	2	0	
Neutrophil count decreased (Hematology)	2	1	0	
Lymphocyte count decreased (Hematology)	2	0	0	
White blood cell count decreased (Hematology)	2	0	0	
Blood creatinine increased (Clinical Chemistry)	11	11	8	
GGT increased (Clinical Chemistry)	5	2	0	
Blood cholesterol increased (Clinical Chemistry)	2	3	0	
Blood bilirubin increased (Clinical Chemistry)	2	1	1	
Lipase increased (Clinical Chemistry)	0	1	2	
AST increased (Clinical Chemistry)	15	7	7	
ALT increased (Clinical Chemistry)	17	8	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival (OS)

End point title	Median Overall Survival (OS)

End point description:

The OS was defined as the time from the first dose of study treatment until the date of death (from any cause and irrespective of any subsequent anti-cancer treatment given). Kaplan-Meier technique was used for calculation. The EE population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	27	19	
Units: Months				
median (confidence interval 95%)	14.0 (10.6 to 17.4)	10.0 (6.7 to 16.1)	14.8 (6.4 to 25.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Bemcentinib at Cycle 1 Day 3

End point title	Maximum Observed Concentration (Cmax) of Bemcentinib at Cycle 1 Day 3

End point description:

The Cmax was defined as maximum observed concentration of bemcentinib. The pharmacokinetics (PK) datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0 hours [h]) at Cycle 1 Day 3 and 4 (24h post dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	29	20	
Units: Nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	187 (± 108)	178 (± 90.9)	169 (± 81.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: OS at 12 Months

End point title	OS at 12 Months

End point description:

The OS was defined as the time from the first dose of study treatment until the date of death (from any cause and irrespective of any subsequent anti-cancer treatment given). The EE population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Up to 12 months following treatment initiation

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	27	19	
Units: Percentage of subjects				
number (confidence interval 95%)	65.9 (50.0 to 77.8)	41.4 (22.4 to 59.5)	50.5 (26.4 to 70.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Bemcentinib at Cycle 1 Day 1

End point title	Cmax of Bemcentinib at Cycle 1 Day 1

End point description:

The Cmax was defined as maximum observed concentration of bemcentinib. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle Day 1 and 2 (24h post dose for Day 1), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: ng/mL				
arithmetic mean (standard deviation)	70.1 (± 42.0)	65.1 (± 34.0)	67.0 (± 34.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (Tmax) of Bemcentinib at Cycle 1 Day 1

End point title	Time to Cmax (Tmax) of Bemcentinib at Cycle 1 Day 1

End point description:

The Tmax was defined as the time taken by bemcentinib to reach Cmax. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle Day 1 and 2 (24h post dose for Day 1), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Hour				
median (full range (min-max))	13.0 (3.99 to 24.0)	14.6 (4.35 to 23.1)	12.0 (4.57 to 23.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Bemcentinib at Steady State

End point title	Cmax of Bemcentinib at Steady State

End point description:

The Cmax was defined as maximum observed concentration of bemcentinib. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle 1 Day 1, 2 (24h post dose for Day 1), 3, and 4 (24h post-dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1 and 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: ng/mL				
arithmetic mean (standard deviation)	270 (± 165)	304 (± 153)	244 (± 134)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Bemcentinib at Steady State

End point title	Tmax of Bemcentinib at Steady State

End point description:

The Tmax was defined as the time taken by bemcentinib to reach Cmax. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle 1 Day 1, 2 (24h post dose for Day 1), 3, and 4 (24h post-dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1 and 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Hour				
median (full range (min-max))	7.55 (2.80 to 13.9)	7.70 (3.40 to 11.5)	7.75 (3.30 to 10.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration Versus Time Curve From Time 0 to 24h Post dose (AUC0-24h) of Bemcentinib at Cycle 1 Day 1

End point title	Area Under the Concentration Versus Time Curve From Time 0 to 24h Post dose (AUC0-24h) of Bemcentinib at Cycle 1 Day 1

End point description:

The AUC0-24h post-dose; that was, within a dosing interval. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle Day 1 and 2 (24h post dose for Day 1), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Nanograms*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	1190 (± 773)	1070 (± 583)	1170 (± 599)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of Bemcentinib at Cycle 1 Day 3

End point title	Tmax of Bemcentinib at Cycle 1 Day 3

End point description:

The Tmax was defined as the time taken by bemcentinib to reach Cmax. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle 1 Day 3 and 4 (24h post dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	29	20	
Units: Hour				
median (full range (min-max))	10.3 (3.37 to 26.2)	11.2 (3.87 to 24.2)	9.86 (4.06 to 24.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24h of Bemcentinib at Steady State

End point title	AUC0-24h of Bemcentinib at Steady State

End point description:

The AUC0-24h post-dose; that was, within a dosing interval. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle 1 Day 1, 2 (24h post dose for Day 1), 3, and 4 (24h post-dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1 and 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: ng*h/mL				
arithmetic mean (standard deviation)	6250 (± 3880)	7090 (± 3620)	5640 (± 3200)	

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24h of Bemcentinib at Cycle 1 Day 3

End point title	AUC0-24h of Bemcentinib at Cycle 1 Day 3

End point description:

The AUC0-24h post-dose; that was, within a dosing interval. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle 1 Day 3 and 4 (24h post dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	29	20	
Units: ng*h/mL				
arithmetic mean (standard deviation)	4210 (± 2480)	4120 (± 2210)	3570 (± 1820)	

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS

End point title	Median PFS

End point description:

The PFS was defined as the time from start of treatment until the date of radiological disease progression (the date on which the confirmed progression was initially observed) or the date of death (whichever was earlier). Kaplan-Meier technique was used for calculation. The EE population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	27	19	
Units: Months				
median (confidence interval 95%)	8.2 (4.1 to 12.4)	6.0 (2.2 to 8.3)	6.0 (2.2 to 14.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Shift From a Normal Baseline to an Abnormal Clinically Significant Electrocardiogram (ECG) Result

End point title	Number of Subjects With Shift From a Normal Baseline to an Abnormal Clinically Significant Electrocardiogram (ECG) Result

End point description:

The number of subjects with abnormal clinically significant ECG result as assessed by physician were reported. All subjects who had a shift from an overall normal ECG result at Baseline to an abnormal clinically significant ECG result as worst post-Baseline value on at least one time point during the study were reported in this endpoint. The ES population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

At baseline and up to end of the study (Approximately 61 months)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Subjects	3	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Vital Signs Abnormalities

End point title	Number of Subjects with Clinically Significant Vital Signs Abnormalities

End point description:

Vital sign parameters consisted of measurements of temperature, resting heart rate, seated blood pressure and respiratory rate. The number of subjects with clinically significant trend in vital signs as assessed by physician were reported. The ES population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number Subjects with Adverse Events (AEs)

End point title	Number Subjects with Adverse Events (AEs)

End point description:

An AE was any untoward medical occurrence in a subject administered a pharmaceutical product and which did not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable or unintended sign, symptom or disease temporally associated with the use of the pharmaceutical product whether or not considered related to the pharmaceutical product. This included any occurrence that was new, an exacerbation of an existing disease (a worsening of the character, frequency or severity of a known condition) or abnormal results of diagnostic procedures, including clinically significant laboratory test abnormalities. The ES population was analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Approximately 61 months (From the date of first observation to the last observation)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Subjects	49	29	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half Life (T1/2) of Bemcentinib at Cycle 1 Day 1

End point title	Elimination Half Life (T1/2) of Bemcentinib at Cycle 1 Day 1

End point description:

The T1/2 was reported. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle Day 1 and 2 (24h post dose for Day 1), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Hours				
arithmetic mean (standard deviation)	109 (± 202)	102 (± 661)	172 (± 206)	

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2 of Bemcentinib at Cycle 1 Day 3

End point title	T1/2 of Bemcentinib at Cycle 1 Day 3

End point description:

The T1/2 was reported. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle 1 Day 3 and 4 (24h post dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	29	20	
Units: Hours				
arithmetic mean (standard deviation)	142 (± 137)	221 (± 353)	103 (± 164)	

Statistical analyses

No statistical analyses for this end point

Secondary: T1/2 of Bemcentinib at Steady State

End point title	T1/2 of Bemcentinib at Steady State

End point description:

The T1/2 was reported. The PK datasets were analyzed.

End point type	Secondary

End point timeframe:

Pre-dose (0h) at Cycle 1 Day 1, 2 (24h post dose for Day 1), 3, and 4 (24h post-dose for Day 3), and 2, 4, 6, and 8h post dose at Cycle 1 Day 1 and 3

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	29	20	
Units: Hours				
arithmetic mean (standard deviation)	181 (± 263)	192 (± 195)	135 (± 89.9)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Approximately 61 months (From the date of first observation to the last observation).	
Adverse event reporting additional description:	
All treatment emergent serious adverse events (SAEs) and Non-SAEs were reported.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Cohort B
Reporting group description:	
This arm included subjects who had a maximum of one prior line of an anti-PD-(L)1 therapy (monotherapy). During the course of study all subjects received at least one dose of bemcentinib and pembrolizumab.	
Reporting group title	Cohort C
Reporting group description:	
This arm included subjects who had a maximum of one prior line of therapy with an anti-PD-(L)1 therapy in combination with a platinum-containing chemotherapy. During the course of study all subjects received at least one dose of bemcentinib and pembrolizumab.	
Reporting group title	Cohort A
Reporting group description:	
This arm included subjects who had a maximum of one prior line of platinum-containing chemotherapy and had not received prior immunotherapy of any kind. During the course of the study all subjects received at least one dose of bemcentinib and pembrolizumab.	

Serious adverse events	Cohort B	Cohort C	Cohort A
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 29 (37.93%)	9 / 20 (45.00%)	29 / 50 (58.00%)
number of deaths (all causes)	2	0	4
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Non-cardiac chest pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (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
Investigations			
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (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			
Femoral neck fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuromyelitis optica spectrum disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (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
Paralysis recurrent laryngeal nerve			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (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
Faecalith			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Immune-mediated hepatitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (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
Chronic kidney disease			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Bone pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 29 (6.90%)	2 / 20 (10.00%)	5 / 50 (10.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Respiratory tract infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
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 pneumococcal			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (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	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
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 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (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			
Dehydration			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (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
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort B	Cohort C	Cohort A
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)	20 / 20 (100.00%)	47 / 50 (94.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Cancer pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	3 / 50 (6.00%)
occurrences (all)	0	1	3
Deep vein thrombosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Varicose vein			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Orthostatic hypotension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Peripheral artery occlusion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	2
Chest pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	9 / 29 (31.03%)	2 / 20 (10.00%)	18 / 50 (36.00%)
occurrences (all)	23	3	41
Chest discomfort			

subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Feeling of body temperature change			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	8 / 29 (27.59%)	7 / 20 (35.00%)	8 / 50 (16.00%)
occurrences (all)	10	9	13
Device related thrombosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	5 / 50 (10.00%)
occurrences (all)	0	1	5
Oedema peripheral			
subjects affected / exposed	4 / 29 (13.79%)	1 / 20 (5.00%)	3 / 50 (6.00%)
occurrences (all)	4	1	4
Pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Peripheral swelling			
subjects affected / exposed	1 / 29 (3.45%)	2 / 20 (10.00%)	0 / 50 (0.00%)
occurrences (all)	1	2	0
Pyrexia			
subjects affected / exposed	6 / 29 (20.69%)	4 / 20 (20.00%)	7 / 50 (14.00%)
occurrences (all)	6	4	8
Suprapubic pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Temperature regulation disorder			

subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	6 / 50 (12.00%)
occurrences (all)	2	0	8
Malaise			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Illness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hunger			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
General physical health deterioration			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Oedema			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Breast pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Erectile dysfunction			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 29 (24.14%)	3 / 20 (15.00%)	12 / 50 (24.00%)
occurrences (all)	7	4	13
Bronchospasm			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Pleuritic pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	8 / 29 (27.59%)	4 / 20 (20.00%)	7 / 50 (14.00%)
occurrences (all)	11	4	11
Rhinorrhoea			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Haemoptysis			
subjects affected / exposed	2 / 29 (6.90%)	3 / 20 (15.00%)	4 / 50 (8.00%)
occurrences (all)	2	3	4
Hiccups			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pneumothorax			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Respiratory tract congestion			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Rhinalgia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dyspnoea exertional			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Sputum discoloured			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Productive cough			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Tachypnoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Persistent depressive disorder			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	3
Confusional state			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Delirium			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0

Depressed mood			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Insomnia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	5 / 50 (10.00%)
occurrences (all)	1	0	5
Adjustment disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences (all)	1	3	3
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	8 / 29 (27.59%)	4 / 20 (20.00%)	17 / 50 (34.00%)
occurrences (all)	18	9	38
Amylase increased			
subjects affected / exposed	2 / 29 (6.90%)	4 / 20 (20.00%)	4 / 50 (8.00%)
occurrences (all)	3	11	9
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 29 (24.14%)	7 / 20 (35.00%)	15 / 50 (30.00%)
occurrences (all)	16	13	36
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 29 (6.90%)	2 / 20 (10.00%)	6 / 50 (12.00%)
occurrences (all)	2	3	8
Blood cholesterol increased			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	3	0	3
Blood creatine increased			

subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	11 / 29 (37.93%)	8 / 20 (40.00%)	11 / 50 (22.00%)
occurrences (all)	23	14	34
Blood folate decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Blood iron decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	2 / 29 (6.90%)	3 / 20 (15.00%)	3 / 50 (6.00%)
occurrences (all)	2	4	4
Computerised tomogram abnormal			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Cortisol decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Electrocardiogram abnormal			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			

subjects affected / exposed	8 / 29 (27.59%)	4 / 20 (20.00%)	7 / 50 (14.00%)
occurrences (all)	11	5	9
Lipase increased			
subjects affected / exposed	1 / 29 (3.45%)	2 / 20 (10.00%)	0 / 50 (0.00%)
occurrences (all)	2	10	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	8
Platelet count decreased			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Neutrophil count decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	3
Urine bilirubin increased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	5 / 50 (10.00%)
occurrences (all)	3	0	9
White blood cell count decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	1	1	1
Clavicle fracture			

subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Upper limb fracture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Radiation skin injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Sinus tachycardia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Pericardial effusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Bundle branch block right			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Monoparesis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Burning sensation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	3 / 50 (6.00%)
occurrences (all)	1	1	3
Hemiparesis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Hypersomnia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Vocal cord paralysis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Neurotoxicity			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 29 (17.24%)	4 / 20 (20.00%)	12 / 50 (24.00%)
occurrences (all)	7	5	19
Lymph node pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Coagulopathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Microcytic anaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	3
Thrombocytopenia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Lymphopenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	4

Ear and labyrinth disorders			
Ear haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Ear pain			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Photopsia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Eyelid ptosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis allergic			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	1	1	1
Gingival bleeding			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Abdominal pain lower			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	3 / 50 (6.00%)
occurrences (all)	2	0	4
Abdominal distension			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	3 / 50 (6.00%)
occurrences (all)	0	1	3
Dry mouth			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	12 / 29 (41.38%)	8 / 20 (40.00%)	21 / 50 (42.00%)
occurrences (all)	20	12	31
Constipation			
subjects affected / exposed	6 / 29 (20.69%)	1 / 20 (5.00%)	7 / 50 (14.00%)
occurrences (all)	6	1	11
Colitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	1
Cheilitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Ascites			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Lip oedema			

subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	2 / 29 (6.90%)	2 / 20 (10.00%)	0 / 50 (0.00%)
occurrences (all)	2	2	0
Pancreatitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Odynophagia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	7 / 29 (24.14%)	5 / 20 (25.00%)	12 / 50 (24.00%)
occurrences (all)	9	7	18
Stomatitis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Toothache			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	6 / 29 (20.69%)	4 / 20 (20.00%)	8 / 50 (16.00%)
occurrences (all)	7	7	10
Poor dental condition			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Regurgitation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

Hyperbilirubinaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	4
Hypertransaminasaemia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	7 / 50 (14.00%)
occurrences (all)	3	1	14
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 29 (13.79%)	3 / 20 (15.00%)	7 / 50 (14.00%)
occurrences (all)	4	4	9
Rash pruritic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Decubitus ulcer			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Dermatitis acneiform			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	5
Dry skin			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Hyperkeratosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Lichen sclerosus			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Night sweats			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Rash			

subjects affected / exposed	3 / 29 (10.34%)	2 / 20 (10.00%)	4 / 50 (8.00%)
occurrences (all)	3	2	6
Rash erythematous			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	1 / 50 (2.00%)
occurrences (all)	0	3	1
Rash macular			
subjects affected / exposed	0 / 29 (0.00%)	2 / 20 (10.00%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Rash maculo-papular			
subjects affected / exposed	2 / 29 (6.90%)	2 / 20 (10.00%)	4 / 50 (8.00%)
occurrences (all)	3	2	7
Skin exfoliation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Skin mass			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Polyuria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Renal colic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

Haematuria			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Renal impairment			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Urinary tract disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Renal failure			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences (all)	1	1	4
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Hypothyroidism			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Diabetes insipidus			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Adrenal insufficiency			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 29 (10.34%)	4 / 20 (20.00%)	7 / 50 (14.00%)
occurrences (all)	3	5	14
Arthritis			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	6
Back pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 20 (10.00%)	7 / 50 (14.00%)
occurrences (all)	0	2	9
Bone pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	3
Flank pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 29 (3.45%)	3 / 20 (15.00%)	2 / 50 (4.00%)
occurrences (all)	1	4	2
Greater trochanteric pain syndrome			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	1 / 29 (3.45%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Musculoskeletal chest pain			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	3 / 50 (6.00%)
occurrences (all)	2	0	3
Musculoskeletal pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	4 / 50 (8.00%)
occurrences (all)	2	0	4
Neck pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Spondylolisthesis			

subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Oral herpes zoster			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 29 (3.45%)	2 / 20 (10.00%)	2 / 50 (4.00%)
occurrences (all)	1	2	2
Lower respiratory tract infection			
subjects affected / exposed	5 / 29 (17.24%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	6	0	2
Gastroenteritis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Impetigo			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Oesophageal candidiasis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	2 / 50 (4.00%)
occurrences (all)	0	1	2

Fungal infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	3 / 29 (10.34%)	3 / 20 (15.00%)	1 / 50 (2.00%)
occurrences (all)	3	4	3
Upper respiratory tract infection			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Fungal skin infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin candida			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	2 / 29 (6.90%)	2 / 20 (10.00%)	2 / 50 (4.00%)
occurrences (all)	3	2	2
Rash pustular			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	4	0	1
Pharyngitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1

Otitis media			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Toxic shock syndrome			
subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Decreased appetite			
subjects affected / exposed	9 / 29 (31.03%)	5 / 20 (25.00%)	16 / 50 (32.00%)
occurrences (all)	10	6	23
Hyperglycaemia			
subjects affected / exposed	3 / 29 (10.34%)	0 / 20 (0.00%)	5 / 50 (10.00%)
occurrences (all)	3	0	9
Hypertriglyceridaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 20 (0.00%)	4 / 50 (8.00%)
occurrences (all)	2	0	5
Hypomagnesaemia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 20 (10.00%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Hyponatraemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	4
Hypophosphataemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 20 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Iron deficiency			

subjects affected / exposed	0 / 29 (0.00%)	1 / 20 (5.00%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 20 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2018	Amendment 5.0: Consolidation of country specific protocols to create a global protocol.
04 December 2018	Amendment 6.0: Addition of Cohort B.
29 April 2019	Amendment 7.0: Revised Cohort B eligibility criteria to enroll patients who have been stable for at least 12 weeks or have had a confirmed partial response or complete response with subsequent progression.
07 October 2019	Amendment 8.0: Addition of Cohort C.
09 April 2020	Amendment 9.0: Revised Cohort B eligibility criteria to allow a maximum of one prior therapy.
07 October 2020	Amendment 10.0: Bemcentinib dose modifications harmonized with pembrolizumab. Time period for toxicity resolution amended.
26 January 2022	Amendment 11.0: Update to align with pembrolizumab standard text (including additional exclusion criteria) and introduce median overall survival (mOS) as a secondary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported