Clinical trial results:
A Phase IIa, Multicenter, Open-Label Study to Assess the Safety and Efficacy of the Combination of BL-8040 and Pembrolizumab in Patients with Metastatic Pancreatic Cancer, the COMBAT study

Summary

EudraCT number	2018-004372-36
Trial protocol	ES
Global end of trial date	06 September 2022

Results information

Result version number	v1 (current)
This version publication date	18 December 2024
First version publication date	18 December 2024

Trial information

Trial identification

Sponsor protocol code	BL-8040.PAC.201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02826486
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BioLineRx Ltd
Sponsor organisation address	Modi’in Technology Park, 2 HaMa'ayan Street, Modi'in, Israel, 7177871
Public contact	VP Clinical & Medical, BioLineRx Ltd, 972 86429100, clinicaltrials@biolinerx.com
Scientific contact	VP Clinical & Medical, BioLineRx Ltd, 972 86429100, clinicaltrials@biolinerx.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	07 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2022
Global end of trial reached?	Yes
Global end of trial date	06 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of BL-8040 in combination with pembrolizumab (Cohort 1) and BL-8040 and pembrolizumab in combination with liposomal irinotecan (Onivyde®)/5-fluorouracil/leucovorin (5-FU/LV) (Cohort 2) in subjects with metastatic pancreatic adenocarcinoma.

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 research.

Only subjects that met all the study inclusion criteria and none of the exclusion criteria were enrolled.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	05 October 2016
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	Israel: 24
Country: Number of subjects enrolled	United States: 35
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Spain: 19
Worldwide total number of subjects	80
EEA total number of subjects	19

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)	38
From 65 to 84 years	40
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in two cohorts: Cohort 1 (C1) and Cohort 2 (C2)
C1: South Korea, United States and Israel; First Patient First Visit (USA): 05 Oct 2016; Last Patient Recruited (USA): 07 Nov 2017
C2: United States, Israel and Spain; First Patient First Visit (Israel): 19 Dec 2018; Last Patient Recruited (USA): 28 Jan 2020

Pre-assignment

Screening details:

Informed consent, inclusion/exclusion criteria, demographics and medical history, MSI/dMMR status, prior and concomitant medications, AEs, ECG, full PE, vital signs, height, ECOG performance status, labs, HIV, HBV and HCV serology, CA 19-9 and CEA, tumor tissue, blood and serum (for biomarkers), CT/MRI. 37/57 (C1) and 43/55 (C2) enrolled/screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: BL-8040 + Pembrolizumab

Arm description:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
Combination Therapy: Combination therapy period begins following monotherapy treatment and consists of:
- Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion)
- Beginning on Day 10, BL-8040 three times a week (given as SC injections)

Arm type	Experimental
Investigational medicinal product name	BL-8040
Investigational medicinal product code	
Other name	Motixafortide (INN)
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
In Combination Therapy period (begins following monotherapy treatment): Beginning on Day 10, BL-8040 three times a week (given as SC injections)

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

Dosage and administration details:

In Combination Therapy period (begins following monotherapy treatment):
Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion)

Arm title	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy

Arm description:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
Combination therapy: Combination therapy period begins following monotherapy treatment and consists

of:
- Chemotherapy: IV Onivyde® 70 mg/m2 over 90 minutes, followed by IV leucovorin (LV) 400 mg/m2 over 30 minutes or according to local standard, followed by IV fluorouracil (5-FU) 2400 mg/m2 over 46 hours, every 2 weeks.
- Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion).
- Beginning on Day 10, BL-8040 twice a week and following the chemotherapy dosing (given by SC injections).

Arm type	Experimental
Investigational medicinal product name	BL-8040
Investigational medicinal product code	
Other name	Motixafortide (INN)
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
In Combination Therapy period (begins following monotherapy treatment): Beginning on Day 10, BL-8040 twice a week and following the chemotherapy dosing (given as SC injections)

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

Dosage and administration details:

In Combination Therapy period (begins following monotherapy treatment):
Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion)

Investigational medicinal product name	Chemotherapy
Investigational medicinal product code	
Other name	Onivyde + leucovorin + fluorouracil
Pharmaceutical forms	Solution for injection/infusion, Powder for concentrate for solution for injection/infusion, Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In Combination therapy period (begins following monotherapy treatment):
IV Onivyde® 70 mg/m2 over 90 minutes, followed by IV leucovorin (LV) 400 mg/m2 over 30 minutes or according to local standard, followed by IV fluorouracil (5-FU) 2400 mg/m2 over 46 hours, every 2 weeks.

Number of subjects in period 1	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy
Started	37	43
Completed	37	43

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: BL-8040 + Pembrolizumab
Reporting group description:	
Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment. Combination Therapy: Combination therapy period begins following monotherapy treatment and consists of: - Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion) - Beginning on Day 10, BL-8040 three times a week (given as SC injections)	
Reporting group title	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy
Reporting group description:	
Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment. Combination therapy: Combination therapy period begins following monotherapy treatment and consists of: - Chemotherapy: IV Onivyde® 70 mg/m2 over 90 minutes, followed by IV leucovorin (LV) 400 mg/m2 over 30 minutes or according to local standard, followed by IV fluorouracil (5-FU) 2400 mg/m2 over 46 hours, every 2 weeks. - Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion). - Beginning on Day 10, BL-8040 twice a week and following the chemotherapy dosing (given by SC injections).	

Reporting group values	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy	Total
Number of subjects	37	43	80
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	63.9	66.3	
standard deviation	± 8.2	± 9.6	-
Gender categorical Units: Subjects			
Female	19	19	38
Male	18	24	42
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	1	2	3
White	33	36	69
More than one race	0	0	0
Unknown or Not Reported	1	3	4

Subject analysis sets

Subject analysis set title	ITT Analysis Set - Cohort 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All data collected for all subjects who were enrolled into Cohort 1 of the study and treated for at least once with monotherapy of BL-8040 (motixafortide). This analysis set served as the principal analysis set for safety inference and for OS and PFS inferences.

Subject analysis set title	ITT Analysis Set - Cohort 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All data collected for all subjects who were enrolled into Cohort 2 of the study and treated for at least once with monotherapy of BL-8040 (motixafortide). This analysis set served as the principal analysis set for safety inference and for OS and PFS inferences.

Subject analysis set title	mITT Analysis Set - Cohort 1
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A subset of the ITT set. This set consisted of data from all Cohort 1 subjects who met all of the below criteria:
• Treated with motixafortide at least once during the monotherapy treatment period, and,
• Underwent at least 1 post-monotherapy CT scan.
The mITT analysis set served as the principal analysis set for efficacy inference of all efficacy endpoints except for the OS and PFS analyses.

Subject analysis set title	mITT Analysis Set - Cohort 2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A subset of the ITT set. This set consisted of data from all Cohort 2 subjects who met all of the below criteria:
• Treated with motixafortide at least once during the monotherapy treatment period, and,
• Started with pembrolizumab and Onivyde®/5-FU/LV treatment thereafter (Cohort 2), and,
• Underwent at least 1 post-monotherapy CT scan.
The mITT analysis set served as the principal analysis set for efficacy inference of all efficacy endpoints except for the OS and PFS analyses.

Reporting group values	ITT Analysis Set - Cohort 1	ITT Analysis Set - Cohort 2	mITT Analysis Set - Cohort 1
Number of subjects	37	43	30
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: years			
arithmetic mean	63.9	66.3	63.4
standard deviation	± 8.2	± 9.6	± 8.9
Gender categorical Units: Subjects			
Female	19	19	18
Male	18	24	12
Race Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			

Reporting group values	mITT Analysis Set - Cohort 2		
Number of subjects	39		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	66.8		
standard deviation	± 9.7		
Gender categorical Units: Subjects			
Female	18		
Male	21		
Race Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	Cohort 1: BL-8040 + Pembrolizumab

Reporting group description:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
Combination Therapy: Combination therapy period begins following monotherapy treatment and consists of:
- Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion)
- Beginning on Day 10, BL-8040 three times a week (given as SC injections)

Reporting group title	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy

Reporting group description:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
Combination therapy: Combination therapy period begins following monotherapy treatment and consists of:
- Chemotherapy: IV Onivyde® 70 mg/m2 over 90 minutes, followed by IV leucovorin (LV) 400 mg/m2 over 30 minutes or according to local standard, followed by IV fluorouracil (5-FU) 2400 mg/m2 over 46 hours, every 2 weeks.
- Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion).
- Beginning on Day 10, BL-8040 twice a week and following the chemotherapy dosing (given by SC injections).

Subject analysis set title	ITT Analysis Set - Cohort 1
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All data collected for all subjects who were enrolled into Cohort 1 of the study and treated for at least once with monotherapy of BL-8040 (motixafortide). This analysis set served as the principal analysis set for safety inference and for OS and PFS inferences.

Subject analysis set title	ITT Analysis Set - Cohort 2
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All data collected for all subjects who were enrolled into Cohort 2 of the study and treated for at least once with monotherapy of BL-8040 (motixafortide). This analysis set served as the principal analysis set for safety inference and for OS and PFS inferences.

Subject analysis set title	mITT Analysis Set - Cohort 1
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A subset of the ITT set. This set consisted of data from all Cohort 1 subjects who met all of the below criteria:
• Treated with motixafortide at least once during the monotherapy treatment period, and,
• Underwent at least 1 post-monotherapy CT scan.
The mITT analysis set served as the principal analysis set for efficacy inference of all efficacy endpoints except for the OS and PFS analyses.

Subject analysis set title	mITT Analysis Set - Cohort 2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A subset of the ITT set. This set consisted of data from all Cohort 2 subjects who met all of the below criteria:
• Treated with motixafortide at least once during the monotherapy treatment period, and,
• Started with pembrolizumab and Onivyde®/5-FU/LV treatment thereafter (Cohort 2), and,
• Underwent at least 1 post-monotherapy CT scan.
The mITT analysis set served as the principal analysis set for efficacy inference of all efficacy endpoints except for the OS and PFS analyses.

Primary: Objective Response Rate (ORR) Assessed by Imaging According to RECIST 1.1 Criteria

End point title	Objective Response Rate (ORR) Assessed by Imaging According to RECIST 1.1 Criteria

End point description:

Response is determined by assessment of target lesions identified in CT or MRI imaging.
The ORR is assessed according to RECIST 1.1, defined as the sum of PRs (Partial Responses) and CRs (Complete Responses) determined according to best response RECIST 1.1 criteria.
PR is defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
CR is defined as disappearance of all target lesions.

End point type	Primary

End point timeframe:

Change in response between screening, end of monotherapy (Day 5), end of cycle 2 (Day 28) and approximately every 63 days until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 24 months.

End point values	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy	ITT Analysis Set - Cohort 1	ITT Analysis Set - Cohort 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	30	39	37	43
Units: Subjects	1	8	1	8

End point values	mITT Analysis Set - Cohort 1	mITT Analysis Set - Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	39		
Units: Subjects	1	8		

Statistical analyses

Statistical analysis title	Statistical Methods

Statistical analysis description:

This was an open-label, Phase IIa two-cohort study to evaluate the two potential treatments regimens. Neither power assessment nor between-cohort formal hypotheses testing were planned for study outcome measures. The primary efficacy endpoint was the ORR. Principal analysis for inference used the mITT Analysis Set. The ORR and its lower 95% one-sided confidence limit (CL) was displayed for each study cohort. Sensitivity analysis was performed for the Intent-to-Treat (ITT) analysis set.

Comparison groups	Cohort 1: BL-8040 + Pembrolizumab v Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	confidence interval
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.3

Notes:

[1] - This was an open-label, Phase IIa two-cohort study to evaluate the safety, tolerability and preliminary efficacy study of two potential treatments regimens. Neither power assessment nor between-cohort formal hypotheses testing were planned for study.

Secondary: Overall Survival

End point title	Overall Survival

End point description:

The length of time elapsed in months from monotherapy Day 1 to death

End point type	Secondary

End point timeframe:

Through study completion, an average of 2 years for cohort of the study, and follow-up until date of death up to 100 weeks.

End point values	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy	ITT Analysis Set - Cohort 1	ITT Analysis Set - Cohort 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	37	43	37	43
Units: Months				
median (confidence interval 95%)	3.3 (2.8 to 7.5)	6.6 (4.5 to 8.7)	3.3 (2.8 to 7.5)	6.6 (4.5 to 8.7)

End point values	mITT Analysis Set - Cohort 1	mITT Analysis Set - Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	39		
Units: Months				
median (confidence interval 95%)	4.5 (3.3 to 8.8)	6.5 (4.4 to 8.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) by Imaging (RECIST 1.1)

End point title	Progression-free Survival (PFS) by Imaging (RECIST 1.1)

End point description:

Progression is determined by assessment of target lesions identified in CT or MRI imaging. Progression is defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.

End point type	Secondary

End point timeframe:

Assessed through study completion, an average of 2 years

End point values	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy	ITT Analysis Set - Cohort 1	ITT Analysis Set - Cohort 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	37	43	37	43
Units: Months				
median (confidence interval 95%)	1.5 (1.5 to 1.8)	3.8 (1.6 to 5.1)	1.5 (1.5 to 1.8)	3.8 (1.6 to 5.1)

End point values	mITT Analysis Set - Cohort 1	mITT Analysis Set - Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	39		
Units: Months				
median (confidence interval 95%)	1.5 (1.5 to 2.5)	3.8 (1.5 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (DC)

End point title	Disease Control (DC)

End point description:

Sum of Partial Response (PR), Complete Response (CR) and Stable Disease

End point type	Secondary

End point timeframe:

Through study completion, an average of 2 years

End point values	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy	ITT Analysis Set - Cohort 1	ITT Analysis Set - Cohort 2
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	37	43	37	43
Units: Subjects	11	25	11	25

End point values	mITT Analysis Set - Cohort 1	mITT Analysis Set - Cohort 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	39		
Units: Subjects	10	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study treatment duration, up to 2 years for each cohort. Cohort 1 and Cohort 2 were conducted sequentially, with Cohort 2 initiated following completion of Cohort 1

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Cohort 1: BL-8040 + Pembrolizumab

Reporting group description:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
Combination Therapy: Combination therapy period begins following monotherapy treatment and consists of:
- Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion)
- Beginning on Day 10, BL-8040 three times a week (given as SC injections)

Reporting group title	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy

Reporting group description:

Monotherapy: BL-8040 1.25 mg/kg subcutaneous (SC) injections daily on Days 1-5 of Week 1 of treatment.
Combination therapy: Combination therapy period begins following monotherapy treatment and consists of:
- Chemotherapy: IV Onivyde® 70 mg/m2 over 90 minutes, followed by IV leucovorin (LV) 400 mg/m2 over 30 minutes or according to local standard, followed by IV fluorouracil (5-FU) 2400 mg/m2 over 46 hours, every 2 weeks.
- Pembrolizumab (Keytruda®) 200 mg once every three weeks (given as a 30 minute IV infusion).
- Beginning on Day 10, BL-8040 twice a week and following the chemotherapy dosing (given by SC injections).

Serious adverse events	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 37 (72.97%)	27 / 43 (62.79%)	
number of deaths (all causes)	5	7	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour compression			

subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 37 (2.70%)	3 / 43 (6.98%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organ failure			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 37 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Genital pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	4 / 37 (10.81%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			

Post procedural haemorrhage			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 37 (10.81%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 37 (2.70%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)	6 / 43 (13.95%)	
occurrences causally related to treatment / all	0 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 37 (0.00%)	4 / 43 (9.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric fistula			

subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric haemorrhage			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 37 (2.70%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 37 (2.70%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute kidney injury			

subjects affected / exposed	0 / 37 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abscess limb			

subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 37 (0.00%)	2 / 43 (4.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort 1: BL-8040 + Pembrolizumab	Cohort 2: BL-8040 + Pembrolizumab + Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 37 (100.00%)	42 / 43 (97.67%)	
Vascular disorders			
Flushing			
subjects affected / exposed	14 / 37 (37.84%)	7 / 43 (16.28%)	
occurrences (all)	27	29	
Hypertension			
subjects affected / exposed	7 / 37 (18.92%)	2 / 43 (4.65%)	
occurrences (all)	30	47	
Hypotension			
subjects affected / exposed	5 / 37 (13.51%)	2 / 43 (4.65%)	
occurrences (all)	10	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 37 (13.51%)	16 / 43 (37.21%)	
occurrences (all)	7	24	
Chills			
subjects affected / exposed	6 / 37 (16.22%)	3 / 43 (6.98%)	
occurrences (all)	12	4	
Fatigue			
subjects affected / exposed	21 / 37 (56.76%)	21 / 43 (48.84%)	
occurrences (all)	33	58	
Injection site bruising			
subjects affected / exposed	5 / 37 (13.51%)	0 / 43 (0.00%)	
occurrences (all)	8	0	
Injection site discomfort			
subjects affected / exposed	2 / 37 (5.41%)	2 / 43 (4.65%)	
occurrences (all)	4	6	
Injection site erythema			
subjects affected / exposed	11 / 37 (29.73%)	5 / 43 (11.63%)	
occurrences (all)	36	7	
Injection site haemorrhage			

subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Injection site induration			
subjects affected / exposed	2 / 37 (5.41%)	4 / 43 (9.30%)	
occurrences (all)	3	5	
Injection site nodule			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Injection site pain			
subjects affected / exposed	22 / 37 (59.46%)	28 / 43 (65.12%)	
occurrences (all)	45	63	
Injection site pruritus			
subjects affected / exposed	13 / 37 (35.14%)	5 / 43 (11.63%)	
occurrences (all)	15	8	
Injection site rash			
subjects affected / exposed	4 / 37 (10.81%)	0 / 43 (0.00%)	
occurrences (all)	5	0	
Injection site reaction			
subjects affected / exposed	8 / 37 (21.62%)	6 / 43 (13.95%)	
occurrences (all)	11	8	
Injection site swelling			
subjects affected / exposed	5 / 37 (13.51%)	1 / 43 (2.33%)	
occurrences (all)	7	1	
Injection site warmth			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Oedema peripheral			
subjects affected / exposed	7 / 37 (18.92%)	7 / 43 (16.28%)	
occurrences (all)	9	10	
Pain			
subjects affected / exposed	2 / 37 (5.41%)	3 / 43 (6.98%)	
occurrences (all)	3	3	
Pyrexia			
subjects affected / exposed	8 / 37 (21.62%)	10 / 43 (23.26%)	
occurrences (all)	21	16	
Influenza like illness			

subjects affected / exposed	0 / 37 (0.00%)	4 / 43 (9.30%)	
occurrences (all)	0	4	
Mucosal inflammation			
subjects affected / exposed	0 / 37 (0.00%)	6 / 43 (13.95%)	
occurrences (all)	0	10	
Oedema			
subjects affected / exposed	0 / 37 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	4	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 37 (0.00%)	6 / 43 (13.95%)	
occurrences (all)	0	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 37 (10.81%)	3 / 43 (6.98%)	
occurrences (all)	5	3	
Dyspnoea			
subjects affected / exposed	11 / 37 (29.73%)	5 / 43 (11.63%)	
occurrences (all)	15	14	
Pleural effusion			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Pulmonary embolism			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 37 (8.11%)	2 / 43 (4.65%)	
occurrences (all)	4	2	
Depression			
subjects affected / exposed	3 / 37 (8.11%)	2 / 43 (4.65%)	
occurrences (all)	4	2	
Insomnia			
subjects affected / exposed	1 / 37 (2.70%)	4 / 43 (9.30%)	
occurrences (all)	1	4	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 37 (8.11%)	6 / 43 (13.95%)	
occurrences (all)	3	9	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 37 (10.81%)	6 / 43 (13.95%)	
occurrences (all)	4	10	
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 37 (18.92%)	5 / 43 (11.63%)	
occurrences (all)	12	6	
Blood bilirubin increased			
subjects affected / exposed	7 / 37 (18.92%)	5 / 43 (11.63%)	
occurrences (all)	11	5	
Blood creatinine increased			
subjects affected / exposed	2 / 37 (5.41%)	3 / 43 (6.98%)	
occurrences (all)	5	7	
Blood glucose increased			
subjects affected / exposed	3 / 37 (8.11%)	0 / 43 (0.00%)	
occurrences (all)	7	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 37 (8.11%)	5 / 43 (11.63%)	
occurrences (all)	3	6	
Platelet count decreased			
subjects affected / exposed	4 / 37 (10.81%)	2 / 43 (4.65%)	
occurrences (all)	4	2	
Weight decreased			
subjects affected / exposed	5 / 37 (13.51%)	9 / 43 (20.93%)	
occurrences (all)	11	20	
White blood cell count increased			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 37 (10.81%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Fall			

subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Infusion related reaction			
subjects affected / exposed	3 / 37 (8.11%)	0 / 43 (0.00%)	
occurrences (all)	6	0	
Skin injury			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 37 (8.11%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Sinus tachycardia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Tachycardia			
subjects affected / exposed	2 / 37 (5.41%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 37 (10.81%)	9 / 43 (20.93%)	
occurrences (all)	4	11	
Dysgeusia			
subjects affected / exposed	3 / 37 (8.11%)	8 / 43 (18.60%)	
occurrences (all)	3	11	
Headache			
subjects affected / exposed	3 / 37 (8.11%)	5 / 43 (11.63%)	
occurrences (all)	4	8	
Neuropathy peripheral			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	1 / 37 (2.70%)	4 / 43 (9.30%)	
occurrences (all)	1	8	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	7 / 37 (18.92%)	14 / 43 (32.56%)	
occurrences (all)	9	42	
Leukocytosis			
subjects affected / exposed	2 / 37 (5.41%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Thrombocytopenia			
subjects affected / exposed	4 / 37 (10.81%)	5 / 43 (11.63%)	
occurrences (all)	8	10	
Neutropenia			
subjects affected / exposed	0 / 37 (0.00%)	5 / 43 (11.63%)	
occurrences (all)	0	7	
Eye disorders			
Visual impairment			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Vitreous floaters			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	1 / 37 (2.70%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 37 (8.11%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Abdominal distension			
subjects affected / exposed	5 / 37 (13.51%)	3 / 43 (6.98%)	
occurrences (all)	5	3	
Abdominal pain			
subjects affected / exposed	14 / 37 (37.84%)	14 / 43 (32.56%)	
occurrences (all)	21	22	
Ascites			
subjects affected / exposed	5 / 37 (13.51%)	2 / 43 (4.65%)	
occurrences (all)	12	2	
Constipation			

subjects affected / exposed	10 / 37 (27.03%)	8 / 43 (18.60%)	
occurrences (all)	17	13	
Diarrhoea			
subjects affected / exposed	10 / 37 (27.03%)	22 / 43 (51.16%)	
occurrences (all)	15	70	
Dyspepsia			
subjects affected / exposed	2 / 37 (5.41%)	4 / 43 (9.30%)	
occurrences (all)	2	5	
Flatulence			
subjects affected / exposed	3 / 37 (8.11%)	4 / 43 (9.30%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	13 / 37 (35.14%)	29 / 43 (67.44%)	
occurrences (all)	21	71	
Rectal haemorrhage			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Stomatitis			
subjects affected / exposed	2 / 37 (5.41%)	3 / 43 (6.98%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	13 / 37 (35.14%)	23 / 43 (53.49%)	
occurrences (all)	29	72	
Abdominal pain upper			
subjects affected / exposed	1 / 37 (2.70%)	4 / 43 (9.30%)	
occurrences (all)	1	4	
Dry mouth			
subjects affected / exposed	1 / 37 (2.70%)	3 / 43 (6.98%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	5 / 37 (13.51%)	8 / 43 (18.60%)	
occurrences (all)	19	11	
Night sweats			
subjects affected / exposed	4 / 37 (10.81%)	3 / 43 (6.98%)	
occurrences (all)	5	3	

Pruritus			
subjects affected / exposed	19 / 37 (51.35%)	15 / 43 (34.88%)	
occurrences (all)	68	44	
Rash			
subjects affected / exposed	12 / 37 (32.43%)	12 / 43 (27.91%)	
occurrences (all)	19	25	
Rash erythematous			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	3 / 37 (8.11%)	2 / 43 (4.65%)	
occurrences (all)	15	9	
Urticaria			
subjects affected / exposed	9 / 37 (24.32%)	2 / 43 (4.65%)	
occurrences (all)	29	11	
Pruritus generalized			
subjects affected / exposed	0 / 37 (0.00%)	14 / 43 (32.56%)	
occurrences (all)	0	20	
Skin hyperpigmentation			
subjects affected / exposed	0 / 37 (0.00%)	14 / 43 (32.56%)	
occurrences (all)	0	20	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 37 (5.41%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Hypothyroidism			
subjects affected / exposed	4 / 37 (10.81%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 37 (16.22%)	5 / 43 (11.63%)	
occurrences (all)	13	7	
Back pain			
subjects affected / exposed	11 / 37 (29.73%)	6 / 43 (13.95%)	
occurrences (all)	14	10	
Muscular weakness			

subjects affected / exposed	4 / 37 (10.81%)	0 / 43 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 37 (5.41%)	2 / 43 (4.65%)	
occurrences (all)	2	2	
Musculoskeletal stiffness			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences (all)	3	1	
Myalgia			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Pain in extremity			
subjects affected / exposed	6 / 37 (16.22%)	2 / 43 (4.65%)	
occurrences (all)	9	5	
Bone pain			
subjects affected / exposed	0 / 37 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Musculoskeletal pain			
subjects affected / exposed	0 / 37 (0.00%)	3 / 43 (6.98%)	
occurrences (all)	0	3	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	2 / 37 (5.41%)	0 / 43 (0.00%)	
occurrences (all)	3	0	
Skin infection			
subjects affected / exposed	2 / 37 (5.41%)	1 / 43 (2.33%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	2 / 37 (5.41%)	3 / 43 (6.98%)	
occurrences (all)	3	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 37 (45.95%)	18 / 43 (41.86%)	
occurrences (all)	22	30	
Dehydration			

subjects affected / exposed	6 / 37 (16.22%)	6 / 43 (13.95%)	
occurrences (all)	8	11	
Hyperglycaemia			
subjects affected / exposed	2 / 37 (5.41%)	3 / 43 (6.98%)	
occurrences (all)	4	6	
Hypoalbuminaemia			
subjects affected / exposed	6 / 37 (16.22%)	4 / 43 (9.30%)	
occurrences (all)	6	12	
Hypokalaemia			
subjects affected / exposed	2 / 37 (5.41%)	9 / 43 (20.93%)	
occurrences (all)	2	22	
Hyponatraemia			
subjects affected / exposed	3 / 37 (8.11%)	6 / 43 (13.95%)	
occurrences (all)	3	9	
Hypomagnesaemia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 43 (6.98%)	
occurrences (all)	1	4	
Hypophosphataemia			
subjects affected / exposed	0 / 37 (0.00%)	4 / 43 (9.30%)	
occurrences (all)	0	6	
Hypothyroidism			
subjects affected / exposed	0 / 37 (0.00%)	6 / 43 (13.95%)	
occurrences (all)	0	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2016	AMENDMENT 1 (Protocol version 2) - submitted in US only (on 12 Aug 2016): - A revision to the definition of a DLT to include Grade 4 (life-threatening) vomiting or diarrhea, Grade 4 electrolyte abnormalities, or Grade 4 systemic reaction systems as well as all other clinically significant, adverse events that were common terminology for adverse events (CTCAE) Grade 3 or higher with the exception of injection site reactions unless they resulted in missing one full cycle of motixafortide treatment. - Inclusion Criterion #5 was revised to clarify what constitutes "one or more prior treatments" in the eligibility criteria. - Exclusion Criteria #7 and #10 were revised to clarify that systemic steroids for baseline adrenal insufficiency were permitted. - Exclusion Criterion #15 was revised to exclude subjects with unstable angina, new onset angina within the last 3 months, myocardial infarction within the last six months, and current congestive heart failure New York Heart Association Class III or higher. - A 14-day time window was added to the termination or early discontinuation study visit
23 July 2018	AMENDMENT 2 (Protocol version 3) - submitted in US only (on 23 July 2018): - The study population was divided into two cohorts: Cohort 1 (pembrolizumab + motixafortide) and Cohort 2 (pembrolizumab + motixafortide + chemotherapy). - The rationale for the addition of chemotherapy in Cohort 2, as well as the rationale for chemotherapy dose and regimen selection, was added. - The protocol was revised to include the additional cohort (Cohort 2). - A second safety interim analysis was added, after 6 subjects from Cohort 2 have completed the first cycle of combination therapy. - Inclusion criteria regarding previous treatments and biopsies were updated to reflect the differences between the two cohorts. - Identity of chemotherapy, its administration, manufacturing, storage, dispensing and returns were added. - information regarding concomitant medication with respect to the chosen chemotherapy was added. • Sample size considerations were revised to include the statistical justification for the selection of the sample size and the null hypothesis response rate, as well as the sample size for Cohort 2. • Inclusion Criteria #5 was revised to clarify what constitutes "one or more prior treatments" in the eligibility criteria. • DLT was clarified to include Grade 4 (life-threatening) vomiting or diarrhea, Grade 4 electrolyte abnormalities, or Grade 4 systemic reactions as well as all other clinically significant AEs that were CTCAE) Grade 3 or higher with the exception of injection site reactions unless they resulted in missing one full cycle of motixafortide treatment. • The optionality was removed from the DNA and RNA assessment. • Clarification was provided that tumor tissue collection from metastasis for tumor and correlative studies assessments and blood for DNA and RNA for correlative studies (only if biopsy was taken at this time point) were for Cohort 1 only - For Cohort 2 only, subjects with bowel obstruction were excluded from entering the trial
21 August 2018	AMENDMENT 3 (Protocol version 3.1) - dated 21-Aug-2018 - not submitted: - The screening period sampling for immunophenotyping, CXCR4 and PD-1 expression, etc was deleted. Sampling for these tests was to take place on Day 1, prior to the first motixafortide dose.

13 March 2019	AMENDMENT 4 (Protocol version 4.0) - submitted in US only (on 14 Mar 2016): - Changes in timing of motixafortide dosing were made to remove the requirement for motixafortide administration to be at least 24 hours after chemotherapy. - Dosing of chemotherapy to allow dosing according to local standard was added. - Collection of microsatellite instability / deficient mismatch repair status if available at screening or testing of these using the biopsy sample if not previously tested was included. - The safety follow-up period was extended to 90 days. - Additional guidance regarding dose modifications relating to overlapping toxicities of the study drugs was provided.
28 June 2019	AMENDMENT 5 (Protocol version 4.1) - approved by AEMPS (RA Spain) on 28 Jun 2019: - Premedication with dexamethasone for the prevention of emesis related to Onivyde® treatment was permitted. - Additional timing for electrocardiogram (ECG) assessment during monotherapy period Predose Day 1 was included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported