Clinical trial results:
A Phase 1b/2, Multicenter, Open-label, Basket Trial to Evaluate the Safety of Talimogene Laherparepvec Injected into Liver Tumors Alone and in Combination with Systemic Pembrolizumab in Phase 1b and to Evaluate the Efficacy and Safety of Intratumoral Talimogene Laherparepvec in Combination with Systemic Pembrolizumab to Treat Subjects with Advanced Solid Tumors in Phase 2 (MASTERKEY 318)

Summary

EudraCT number	2014-005386-67
Trial protocol	BE DE AT PL
Global end of trial date	11 July 2023

Results information

Result version number	v2
This version publication date	30 August 2024
First version publication date	14 June 2024
Version creation reason	• Correction of full data set One subject with TCID50 result that had different parameter category assigned.

Trial information

Trial identification

Sponsor protocol code	20140318

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
Public contact	Study Director, Amgen Inc., +1 8665726436, medinfo@amgen.com
Scientific contact	Study Director, Amgen Inc., +1 8665726436, medinfo@amgen.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	11 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In Part 1, the main objective was to evaluate, as assessed by the incidence of dose-limiting toxicities (DLTs) in participants with liver metastases (non- hepatocellular carcinoma [HCC]) & participants with primary HCC in the maximum tolerated volume (monotherapy cohorts) and maximum tolerated concentration (MTC) of intrahepatic injection of talimogene laherparepvec into liver tumors (monotherapy and combination cohorts) in combination with systemic intravenous (IV) administration of pembrolizumab (combination cohorts).

In Part 2, the main objectives were to evaluate the efficacy, as assessed by objective response rate (ORR) of intratumoral injection of talimogene laherparepvec in combination with systemic IV administration of pembrolizumab, separately, for each non-HCC tumor type and primary HCC with and without viral hepatitis and to evaluate safety separately for each tumor type as assessed by incidence of treatment-emergent and treatment-related adverse events, including DLTs.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2016
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	Korea, Republic of: 15
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Spain: 58
Country: Number of subjects enrolled	Switzerland: 18
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Australia: 3
Worldwide total number of subjects	127
EEA total number of subjects	70

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)	84
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

127 participants were enrolled at 22 centers in Australia, Europe, South Korea and the United States from February 2016 to July 2023. As of protocol amendment 6 (dated 26 October 2021), intrahepatic injections of talimogene laherparepvec were no longer performed.

Pre-assignment

Screening details:

Of the 190 participants screened, 127 participants were enrolled and received study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Monotherapy Group A

Arm description:

Participants with non-hepatocellular carcinoma (non-HCC) were administered talimogene laherparepvec.

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Initial concentration of 10^6 plaque forming unit (PFU)/mL in a volume of up to 4mL in Cohorts 1 & 2 and up to a volume of 8 mL in Cohorts 3 & 4 on Day 1 of the first 21-day cycle. The concentration in the second and subsequent 21-day cycles were 10^7 (Cohorts 1 & 4) or 10^8 PFU/mL (Cohorts 2 & 3).

Arm title	Part 1: Monotherapy Group B

Arm description:

Participants with HCC were administered talimogene laherparepvec.

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Initial concentration of 10^6 PFU/mL in a volume of up to 4mL in Cohorts 1 & 2 and up to a volume of 8 mL in Cohorts 3 & 4 on Day 1 of the first 21-day cycle. The concentration in the second and subsequent 21-day cycles were 10^7 (Cohorts 1 & 4) or 10^8 PFU/mL (Cohorts 2 & 3).

Arm title	Part 1: Combination Therapy Group A

Arm description:

Participants with non-HCC were administered talimogene laherparepvec and pembrolizumab.

Arm type	Experimental

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

Dosage and administration details:

200 mg on Day 1 of each 21-day cycle.

Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Initial concentration of 10^6 PFU/mL in a volume of up to 4mL in Cohorts 5 & 6 on Day 1 of the first 21-day cycle. The concentration in the second and subsequent 21-day cycles were 10^7 (Cohort 5) or 10^8 PFU/mL (Cohorts 6).

Arm title	Part 1: Combination Therapy Group B

Arm description:

Participants with HCC were administered talimogene laherparepvec and pembrolizumab.

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

Dosage and administration details:

200 mg on Day 1 of each 21-day cycle.

Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Initial concentration of 10^6 PFU/mL in a volume of up to 4mL in Cohorts 5, 6a (participants without viral hepatitis) and 6b (participants with well controlled viral hepatitis) on Day 1 of the first 21-day cycle. The concentration in the second and subsequent 21-day cycles were 10^7 (Cohort 5) or 10^8 PFU/mL (Cohorts 6a and 6b).

Arm title	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)

Arm description:

Participants with HRBC were administered talimogene laherparepvec and pembrolizumab.

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

Dosage and administration details:

200 mg on Day 1 of each 21-day cycle.

Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection

Routes of administration	Intralesional use

Dosage and administration details:

At the maximum tolerated concentration (MTC) and maximum tolerated volume (MTV) identified in Part 1 on Day 1 of each 21-day cycle.

Arm title	Part 2: Triple Negative Breast Cancer (TNBC)

Arm description:

Participants with TNBC were administered talimogene laherparepvec and pembrolizumab.

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

At the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle.

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

Dosage and administration details:

200 mg on Day 1 of each 21-day cycle.

Arm title	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)

Arm description:

Participants with CSCC were administered talimogene laherparepvec and pembrolizumab.

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

Dosage and administration details:

200 mg on Day 1 of each 21-day cycle.

Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

At the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle.

Arm title	Part 2: Basal Cell Carcinoma (BCC)

Arm description:

Participants with BCC were administered talimogene laherparepvec and pembrolizumab.

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

Dosage and administration details: 200 mg on Day 1 of each 21-day cycle.	
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use
Dosage and administration details: At the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle.	
Arm title	Part 2: Colorectal Adenocarcinoma (CRC)
Arm description: Participants with CRC were administered talimogene laherparepvec and pembrolizumab.	
Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 200 mg on Day 1 of each 21-day cycle.	
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use
Dosage and administration details: At the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle.	

Number of subjects in period 1	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A
Started	23	5	24
Received Talimogene Laherparepvec	23	5	24
Received Pembrolizumab	0	0 [1]	24
Completed	0	1	1
Not completed	23	4	23
Adverse event, serious fatal	21	3	22
Consent withdrawn by subject	2	-	1
Lost to follow-up	-	1	-

Number of subjects in period 1	Part 1: Combination Therapy Group B	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)
Started	22	10	18
Received Talimogene Laherparepvec	22	10	18
Received Pembrolizumab	22	10	18

Completed	4	1	1
Not completed	18	9	17
Adverse event, serious fatal	14	8	12
Consent withdrawn by subject	4	1	3
Lost to follow-up	-	-	2

Number of subjects in period 1	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)	Part 2: Colorectal Adenocarcinoma (CRC)
Started	10	5	10
Received Talimogene Laherparepvec	10	5	10
Received Pembrolizumab	10	5	10
Completed	1	1	1
Not completed	9	4	9
Adverse event, serious fatal	5	4	8
Consent withdrawn by subject	4	-	1
Lost to follow-up	-	-	-

Notes:

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

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Monotherapy Group A
Reporting group description:	
Participants with non-hepatocellular carcinoma (non-HCC) were administered talimogene laherparepvec.	
Reporting group title	Part 1: Monotherapy Group B
Reporting group description:	
Participants with HCC were administered talimogene laherparepvec.	
Reporting group title	Part 1: Combination Therapy Group A
Reporting group description:	
Participants with non-HCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 1: Combination Therapy Group B
Reporting group description:	
Participants with HCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)
Reporting group description:	
Participants with HRBC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Triple Negative Breast Cancer (TNBC)
Reporting group description:	
Participants with TNBC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)
Reporting group description:	
Participants with CSCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Basal Cell Carcinoma (BCC)
Reporting group description:	
Participants with BCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Colorectal Adenocarcinoma (CRC)
Reporting group description:	
Participants with CRC were administered talimogene laherparepvec and pembrolizumab.	

Reporting group values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A
Number of subjects	23	5	24
Age Categorical Units:			
18 - 64 years	16	3	17
65 - 74 years	7	2	5
75 - 84 years	0	0	2
>= 85 years	0	0	0
Age continuous Units: years			
arithmetic mean	56.8	61.2	56.7
standard deviation	± 11.4	± 8.6	± 12.6
Sex: Female, Male Units:			
Female	11	2	10
Male	12	3	14

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	0	1
Not Hispanic or Latino	21	5	23
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	1	0
Black or African American	1	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	20	4	23
Other	0	0	1

Reporting group values	Part 1: Combination Therapy Group B	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)
Number of subjects	22	10	18
Age Categorical Units:			
18 - 64 years	10	8	15
65 - 74 years	8	2	2
75 - 84 years	4	0	1
>= 85 years	0	0	0
Age continuous Units: years			
arithmetic mean	64.0	53.4	52.3
standard deviation	± 13.7	± 9.7	± 12.2
Sex: Female, Male Units:			
Female	5	10	18
Male	17	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	2
Not Hispanic or Latino	21	10	16
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	8	0	3
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	14	10	15
Other	0	0	0

Reporting group values	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)	Part 2: Colorectal Adenocarcinoma (CRC)
Number of subjects	10	5	10

Age Categorical Units:			
18 - 64 years	5	4	6
65 - 74 years	2	1	4
75 - 84 years	3	0	0
>= 85 years	0	0	0
Age continuous Units: years			
arithmetic mean	62.6	57.6	55.7
standard deviation	± 15.1	± 8.4	± 14.8
Sex: Female, Male Units:			
Female	3	2	4
Male	7	3	6
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	9	4	10
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	3	1	1
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	7	4	9
Other	0	0	0

Reporting group values	Total		
Number of subjects	127		
Age Categorical Units:			
18 - 64 years	84		
65 - 74 years	33		
75 - 84 years	10		
>= 85 years	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units:			
Female	65		
Male	62		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	8		
Not Hispanic or Latino	119		
Unknown or Not Reported	0		
Race/Ethnicity, Customized			

Units: Subjects			
American Indian or Alaska Native	0		
Asian	19		
Black or African American	1		
Native Hawaiian or Other Pacific Islander	0		
White	106		
Other	1		

End points

End points reporting groups

Reporting group title	Part 1: Monotherapy Group A
Reporting group description: Participants with non-hepatocellular carcinoma (non-HCC) were administered talimogene laherparepvec.	
Reporting group title	Part 1: Monotherapy Group B
Reporting group description: Participants with HCC were administered talimogene laherparepvec.	
Reporting group title	Part 1: Combination Therapy Group A
Reporting group description: Participants with non-HCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 1: Combination Therapy Group B
Reporting group description: Participants with HCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)
Reporting group description: Participants with HRBC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Triple Negative Breast Cancer (TNBC)
Reporting group description: Participants with TNBC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)
Reporting group description: Participants with CSCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Basal Cell Carcinoma (BCC)
Reporting group description: Participants with BCC were administered talimogene laherparepvec and pembrolizumab.	
Reporting group title	Part 2: Colorectal Adenocarcinoma (CRC)
Reporting group description: Participants with CRC were administered talimogene laherparepvec and pembrolizumab.	

Primary: Part 2 Only: Objective Response Rate (ORR) per Modified Immune-related Response Criteria Simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST)

End point title	Part 2 Only: Objective Response Rate (ORR) per Modified Immune-related Response Criteria Simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST)[1][2]

End point description:

ORR was defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) per modified irRC-RECIST.

- CR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- PR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.

Full Analysis Set (Part 2): Included all participants in Part 2 who received at least 1 dose of talimogene laherparepvec and at least 1 dose of pembrolizumab in combination.

End point type	Primary

End point timeframe:

Up to 154 weeks

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 comparative statistical analyses were planned.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: 'ORR' is a primary endpoint for Part 2 and a secondary endpoint for Part 1.

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: percentage of participants				
number (confidence interval 95%)	10.0 (0.3 to 44.5)	16.7 (3.6 to 41.4)	10.0 (0.3 to 44.5)	20.0 (0.5 to 71.6)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 30.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Experienced a Dose Limiting Toxicity (DLT)

End point title	Number of Participants Who Experienced a Dose Limiting Toxicity (DLT)[3]

End point description:

All toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:
- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to adverse event (AE)

The occurrence of specific pre-defined toxicities during the DLT evaluation period were considered a DLT if judged by the investigator to be related to talimogene laherparepvec and/or pembrolizumab.

All Grade 5 toxicities, intolerable toxicities that lead to permanent discontinuation of talimogene laherparepvec and/or pembrolizumab and Grade 3 or higher AEs related to talimogene laherparepvec and/or pembrolizumab that resulted in a study treatment delay by > 2 weeks were considered DLTs.

The analysis set used was the DLT analysis set.

End point type	Primary

End point timeframe:

Cycle 1 and Cycle 2: Day 1 to Day 21

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No comparative statistical analyses were planned.

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	5	20	19
Units: participants	2	0	1	0

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	11	5	4
Units: participants	1	0	0	0

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2 Only: Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)

End point title	Part 2 Only: Number of Participants Who Experienced a Treatment-emergent Adverse Event (TEAE)[4][5]

End point description:

A TEAE was defined as an event that emerged during treatment, having been absent pretreatment, or worsened relative to the pretreatment state.

A treatment-related TEAE was defined as a TEAE that was suspected to be related to the study treatment.

Safety Analysis Set (Part 2): Included all participants in Part 2 who have received at least 1 dose of talimogene laherparepvec or at least 1 dose of pembrolizumab.

End point type	Primary

End point timeframe:

Day 1 to 30 days post-last dose of talimogene laherparepvec or pembrolizumab, whichever is later. The maximum duration of talimogene laherparepvec treatment was 102.4 weeks and pembrolizumab treatment was 109.3 weeks in Part 2.

Notes:

[4] - 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 comparative statistical analyses were planned.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: 'Number of Participants Who Experienced a TEAE' is a primary endpoint for Part 2 and a secondary endpoint for Part 1.

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: participants				
TEAEs	10	17	9	5
Treatment-related TEAEs	10	12	4	5

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
TEAEs	10			
Treatment-related TEAEs	10			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 Only: ORR per Modified irRC-RECIST

End point title	Part 1 Only: ORR per Modified irRC-RECIST[6]

End point description:

ORR was defined as the percentage of participants with a best overall response of CR or PR per modified irRC-RECIST.

- CR: Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- PR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.

Full Analysis Set (Part 1): Included all participants in Part 1 who received at least 1 dose of talimogene laherparepvec in monotherapy and combination cohorts and at least 1 dose of pembrolizumab in combination cohorts.

End point type	Secondary

End point timeframe:

Up to 297 weeks

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: 'ORR' is a primary endpoint for Part 2 and a secondary endpoint for Part 1.

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 14.8)	0.0 (0.0 to 52.2)	8.3 (1.0 to 27.0)	13.6 (2.9 to 34.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (BOR) per Modified irRC-RECIST

End point title	Best Overall Response (BOR) per Modified irRC-RECIST

End point description:

BOR was defined as the number of participants with a best visit response in following order: CR, PR, stable disease (SD), progressive disease (PD), or unevaluable (UE) per modified irRC-RECIST.

- CR: Disappearance of all lesions and confirmation by assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- PR: Decrease in tumor burden ≥30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.
- SD: Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD.
- PD: Increase in tumor burden ≥ 20 % and at least 5 mm absolute increase relative to nadir confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented PD.
- UE: Any lesion present at baseline which was not assessed or was unable to be evaluated.

Full Analysis Set

End point type	Secondary

End point timeframe:

Up to 297 weeks

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: participants				
CR	0	0	0	0
PR	0	0	2	3
SD	1	1	4	6
PD	7	1	10	3
UE	13	3	7	10
Not Done	2	0	1	0

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: participants				
CR	0	2	0	0
PR	1	1	1	1
SD	1	1	1	2
PD	3	5	2	0
UE	5	6	4	2
Not Done	0	3	2	0

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
CR	0			
PR	0			
SD	3			
PD	1			
UE	5			
Not Done	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response Rate (DRR) per Modified irRC-RECIST

End point title	Durable Response Rate (DRR) per Modified irRC-RECIST

End point description:

DRR per modified irRC-RECIST was defined as the percentage of participants with an objective response (CR/PR) with a duration of response of at least 6 months.

- CR: Disappearance of all lesions and confirmation by assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- PR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.

Full Analysis Set: Included all participants who received at least 1 dose of talimogene laherparepvec in monotherapy and combination cohorts and at least 1 dose of pembrolizumab in combination cohorts in Part 1 and Part 2.

End point type	Secondary

End point timeframe:

Up to 297 weeks

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 14.8)	0.0 (0.0 to 52.2)	8.3 (1.0 to 27.0)	9.1 (1.1 to 29.2)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: percentage of participants				
number (confidence interval 95%)	10.0 (0.3 to 44.5)	11.1 (1.4 to 34.7)	10.0 (0.3 to 44.5)	20.0 (0.5 to 71.6)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 30.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per Modified irRC-RECIST

End point title	Duration of Response (DOR) per Modified irRC-RECIST

End point description:

DOR per modified irRC-RECIST was defined as time from date of initial response (CR/PR) that was confirmed to earlier of PD or death. Estimated using Kaplan-Meier method.
- CR: Disappearance of all lesions confirmed by assessment ≥ 28 days from date first documented. Any pathological lymph nodes must have reduced in short axis to < 10 mm.
- PR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by consecutive assessment at least 28 days after first documentation.
- PD: Increase in tumor burden ≥ 20 % and at least 5 mm absolute increase relative to nadir confirmation by a repeat, consecutive assessment no less than 28 days from date first documented PD.

Full Analysis Set: Included all participants who received at least 1 dose of talimogene laherparepvec in monotherapy and combination cohorts and at least 1 dose of pembrolizumab in combination cohorts in Part 1 and Part 2. Only participants who had a BOR of CR/PR were included.

Values of 9999.9 indicate no data available.

End point type	Secondary

End point timeframe:

Up to 297 weeks

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[7]	0[8]	2	3
Units: months				
median (confidence interval 95%)	(to)	(to)	16.8 (12.2 to 9999.9)	8.9 (4.3 to 9999.9)

Notes:

[7] - Only participants that had a response and subsequently had PD/death were included.

[8] - Only participants that had a response and subsequently had PD/death were included.

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	3	1	1
Units: months				
median (confidence interval 95%)	9999.9 (9999.9 to 9999.9)	23.1 (5.1 to 9999.9)	9999.9 (9999.9 to 9999.9)	9999.9 (9999.9 to 9999.9)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[9] - Only participants that had a response and subsequently had PD/death were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per Modified irRC-RECIST

End point title	Disease Control Rate (DCR) per Modified irRC-RECIST

End point description:

DCR per modified irRC-RECIST was defined as percentage of participants that had a BOR in 1 of the following: CR, PR or SD.

- CR: Disappearance of all lesions and confirmation by assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- PR: Decrease in tumor burden ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.
- SD: Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD.

Full Analysis Set: Included all participants who received at least 1 dose of talimogene laherparepvec in monotherapy and combination cohorts and at least 1 dose of pembrolizumab in combination cohorts in Part 1 and Part 2.

End point type	Secondary

End point timeframe:

Up to 297 weeks

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: percentage of participants				
number (confidence interval 95%)	4.3 (0.1 to 21.9)	20.0 (0.5 to 71.6)	25.0 (9.8 to 46.7)	40.9 (20.7 to 63.6)

End point values	Part 2: Hormone Receptor	Part 2: Triple Negative Breast Cancer	Part 2: Cutaneous Squamous Cell	Part 2: Basal Cell Carcinoma (BCC)

	Positive Breast Cancer (HRBC)	(TNBC)	Carcinoma (CSCC)	
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: percentage of participants				
number (confidence interval 95%)	20.0 (2.5 to 55.6)	22.2 (6.4 to 47.6)	20.0 (2.5 to 55.6)	60.0 (14.7 to 94.7)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	30.0 (6.7 to 65.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Modified irRC-RECIST

End point title	Progression Free Survival (PFS) per Modified irRC-RECIST

End point description:

PFS was defined as the time from first dose to the date of first of confirmed PD per modified irRC-RECIST criteria, or death, whichever occurs first. PFS was estimated using the Kaplan-Meier method. Participants that did not have an event of death or disease progression were censored at the latter of their last evaluable tumor assessment date or first dose date.

- PD: Increase in tumor burden ≥ 20 % and at least 5 mm absolute increase relative to nadir confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented PD.

Full Analysis Set: Included all participants who received at least 1 dose of talimogene laherparepvec in monotherapy and combination cohorts and at least 1 dose of pembrolizumab in combination cohorts in Part 1 and Part 2.

Values of 9999.9 indicate no data available.

End point type	Secondary

End point timeframe:

Up to 297 weeks

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: months				
median (confidence interval 95%)	2.3 (1.9 to 9.0)	3.9 (1.9 to 9999.9)	2.0 (1.9 to 6.2)	8.1 (3.2 to 13.2)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: months				
median (confidence interval 95%)	6.1 (1.6 to 20.5)	2.9 (1.2 to 10.2)	5.4 (2.2 to 9999.9)	16.4 (5.4 to 9999.9)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: months				
median (confidence interval 95%)	8.8 (2.4 to 12.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of first dose date to the date of death from any cause. OS time was censored at the last date the participant was known to be alive when the confirmation of death was absent or unknown, or at the date 24 months after the last participant enrolled if the last known to be alive/death date was beyond it. One month = 365.25/12 days. OS was estimated using the Kaplan-Meier method.

Full Analysis Set: Included all participants who received at least 1 dose of talimogene laherparepvec in monotherapy and combination cohorts and at least 1 dose of pembrolizumab in combination cohorts in Part 1 and Part 2.

Values of 9999.9 indicates no data available.

End point type	Secondary

End point timeframe:

Up to 297 weeks

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: months				
median (confidence interval 95%)	8.7 (2.7 to 17.1)	9.1 (3.9 to 9999.9)	7.8 (4.4 to 14.2)	12.8 (6.8 to 29.5)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: months				
median (confidence interval 95%)	9.1 (2.4 to 20.5)	10.2 (2.7 to 27.2)	9.6 (2.3 to 9999.9)	16.4 (5.4 to 9999.9)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: months				
median (confidence interval 95%)	11.2 (2.4 to 18.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 Only: Number of Participants Who Experienced a TEAE

End point title	Part 1 Only: Number of Participants Who Experienced a

End point description:

A TEAE was defined as an event that emerged during treatment, having been absent pretreatment, or worsened relative to the pretreatment state.

A treatment-related TEAE was defined as a TEAE that was suspected to be related to the study treatment.

Safety Analysis Set (Part 1): Included all participants in Part 1 who have received at least 1 dose of talimogene laherparepvec or at least 1 dose of pembrolizumab.

End point type	Secondary

End point timeframe:

Day 1 to 30 days post-last dose of talimogene laherparepvec or pembrolizumab, whichever is later. The maximum duration of talimogene laherparepvec treatment was 34.1 weeks and pembrolizumab treatment was 98.3 weeks in Part 1.

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: 'Number of Participants Who Experienced a TEAE' is a primary endpoint for Part 2 and a secondary endpoint for Part 1.

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: participants				
TEAEs	23	5	24	21
Treatment-related TEAEs	23	5	22	20

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec Deoxyribonucleic Acid (DNA) in Blood

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec Deoxyribonucleic Acid (DNA) in Blood

End point description:

Blood samples were tested using real-time polymerase chain reaction (qPCR). Detectable DNA was defined as a positive result by qPCR analysis.

Blood Evaluable Analysis Set: Included all participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one post dose blood sample collected.

End point type	Secondary

End point timeframe:

Week 1 to Week 10

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: percentage of participants				
number (confidence interval 95%)	100.0 (85.2 to 100.0)	100.0 (47.8 to 100.0)	100.0 (85.8 to 100.0)	95.5 (77.2 to 99.9)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: percentage of participants				
number (confidence interval 95%)	90.0 (55.5 to 99.7)	88.9 (65.3 to 98.6)	50.0 (18.7 to 81.3)	60.0 (14.7 to 94.7)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	100.0 (69.2 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec DNA in Urine

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec DNA in Urine

End point description:

Urine samples were tested using qPCR. Detectable DNA was defined as a positive result by qPCR analysis.

Urine Evaluable Analysis Set: Included all participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one post dose urine sample collected.

End point type	Secondary

End point timeframe:

Week 1 to Week 10

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: percentage of participants				
number (confidence interval 95%)	34.8 (16.4 to 57.3)	40.0 (5.3 to 85.3)	37.5 (18.8 to 59.4)	54.5 (32.2 to 75.6)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	18	10	5
Units: percentage of participants				
number (confidence interval 95%)	10.0 (0.3 to 44.5)	27.8 (9.7 to 53.5)	20.0 (2.5 to 55.6)	0.0 (0.0 to 52.2)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	30.0 (6.7 to 65.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clearance of Talimogene Laherparepvec in Blood

End point title	Percentage of Participants with Clearance of Talimogene Laherparepvec in Blood

End point description:

Blood samples were tested using real-time qPCR.

A participant was defined as having cleared talimogene laherparepvec if a negative qPCR in a sample was obtained following a prior positive test and if there were no subsequent positive test results in the same cycle.

Blood Clearance Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least 2 post dose samples, collected within the same dosing cycle. Participants must have had at least 1 positive sample and at least 1 subsequent sample at any time during the cycle. All participants included in the overall number of participants contributed analyzed data.

Values of 9999.9 indicate no data available. Values of 99999.9 indicate N = 0.

End point type	Secondary

End point timeframe:

Cycles 2, 3 and 4: Day 1 pre-dose. Each cycle was 21 days.

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23[11]	5[12]	24[13]	21[14]
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 2, Day 1 Pre-dose	73.9 (51.6 to 89.8)	100.0 (47.8 to 100.0)	52.2 (30.6 to 73.2)	95.2 (76.2 to 99.9)
Cycle 3, Day 1 Pre-dose	66.7 (41.0 to 86.7)	100.0 (47.8 to 100.0)	70.0 (45.7 to 88.1)	100.0 (81.5 to 100.0)
Cycle 4, Day 1 Pre-dose	66.7 (9.4 to 99.2)	99999.9 (99999.9 to 99999.9)	37.5 (8.5 to 75.5)	99999.9 (99999.9 to 99999.9)

Notes:

[11] - Cycle 2 N = 23
Cycle 3 N = 18
Cycle 4 N = 3
[12] - Cycle 2 N = 5
Cycle 3 N = 5
Cycle 4 N = 0
[13] - Cycle 2 N = 23
Cycle 3 N = 20
Cycle 4 N = 8
[14] - Cycle 2 N = 21
Cycle 3 N = 18
Cycle 4 N = 0

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9[15]	16[16]	5[17]	3[18]
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 2, Day 1 Pre-dose	85.7 (42.1 to 99.6)	80.0 (51.9 to 95.7)	66.7 (9.4 to 99.2)	66.7 (9.4 to 99.2)
Cycle 3, Day 1 Pre-dose	77.8 (40.0 to 97.2)	75.0 (42.8 to 94.5)	75.0 (19.4 to 99.4)	100.0 (15.8 to 100.0)
Cycle 4, Day 1 Pre-dose	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)

Notes:

[15] - Cycle 2 N = 7
Cycle 3 N = 9
Cycle 4 N = 0
[16] - Cycle 2 N = 15
Cycle 3 N = 12

Cycle 4 N = 0

[17] - Cycle 2 N = 3
Cycle 3 N = 4
Cycle 4 N = 0

[18] - Cycle 2 N = 3
Cycle 3 N = 2
Cycle 4 N = 0

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10[19]			
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 2, Day 1 Pre-dose	60.0 (26.2 to 87.8)			
Cycle 3, Day 1 Pre-dose	70.0 (34.8 to 93.3)			
Cycle 4, Day 1 Pre-dose	100.0 (2.5 to 100.0)			

Notes:

[19] - Cycle 2 N = 10
Cycle 3 N = 10
Cycle 4 N = 1

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clearance of Talimogene Laherparepvec in Urine

End point title	Percentage of Participants with Clearance of Talimogene Laherparepvec in Urine

End point description:

Urine samples were tested using qPCR.

A participant was defined as having cleared talimogene laherparepvec if a negative qPCR in a sample was obtained following a prior positive test and if there were no subsequent positive test results in the same cycle.

Urine Clearance Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least 2 post dose samples, collected within the same dosing cycle. Participants must have had at least 1 positive sample and at least 1 subsequent sample at any time during the cycle.

Values of 9999.9 indicate no data available.
Values of 99999.9 indicate N = 0.

End point type	Secondary

End point timeframe:

Cycles 2, 3 and 4: Day 1 pre-dose. Each cycle was 21 days.

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[20]	2[21]	9[22]	11[23]
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 2, Day 1 Pre-dose	100.0 (29.2 to 100.0)	100.0 (2.5 to 100.0)	80.0 (28.4 to 99.5)	100.0 (29.2 to 100.0)
Cycle 3, Day 1 Pre-dose	100.0 (59.0 to 100.0)	100.0 (2.5 to 100.0)	100.0 (47.8 to 100.0)	100.0 (69.2 to 100.0)
Cycle 4, Day 1 Pre-dose	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)

Notes:

[20] - Cycle 2 N = 3
Cycle 3 N = 7
Cycle 4 N = 0
[21] - Cycle 2 N = 1
Cycle 3 N = 1
Cycle 4 N = 0
[22] - Cycle 2 N = 5
Cycle 3 N = 5
Cycle 4 N = 0
[23] - Cycle 2 N = 3
Cycle 3 N = 10
Cycle 4 N = 0

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1[24]	5[25]	1[26]	0[27]
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 2, Day 1 Pre-dose	99999.9 (99999.9 to 99999.9)	100.0 (29.2 to 100.0)	0.0 (0.0 to 97.5)	(to)
Cycle 3, Day 1 Pre-dose	100.0 (2.5 to 100.0)	100.0 (29.2 to 100.0)	99999.9 (99999.9 to 99999.9)	(to)
Cycle 4, Day 1 Pre-dose	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)	99999.9 (99999.9 to 99999.9)	(to)

Notes:

[24] - Cycle 2 N = 0
Cycle 3 N = 1
Cycle 4 N = 0
[25] - Cycle 2 N = 3
Cycle 3 N = 3
Cycle 4 N = 0
[26] - Cycle 2 N = 1
Cycle 3 N = 1
Cycle 4 N = 0
[27] - No participants had evaluable data.

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			

Subject group type	Reporting group			
Number of subjects analysed	3[28]			
Units: percentage of participants				
number (confidence interval 95%)				
Cycle 2, Day 1 Pre-dose	100.0 (15.8 to 100.0)			
Cycle 3, Day 1 Pre-dose	100.0 (15.8 to 100.0)			
Cycle 4, Day 1 Pre-dose	99999.9 (99999.9 to 99999.9)			

Notes:

[28] - Cycle 2 N = 2
Cycle 3 N = 2
Cycle 4 N = 0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec DNA at the Surface of Injection Site

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec DNA at the Surface of Injection Site

End point description:

The percentage of participants with positive qPCR and subsequent positive plaque assays were evaluated from swabs of skin surface of injections. Detectable DNA was defined as a positive result by qPCR analysis.

Skin Surface of Injections Evaluable Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one swab collected from the skin surface of injections.

End point type	Secondary

End point timeframe:

Week 1 to Week 10

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: percentage of participants				
number (confidence interval 95%)	69.6 (47.1 to 86.8)	60.0 (14.7 to 94.7)	79.2 (57.8 to 92.9)	72.7 (49.8 to 89.3)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	16	10	4

Units: percentage of participants				
number (confidence interval 95%)	60.0 (26.2 to 87.8)	68.8 (41.3 to 89.0)	80.0 (44.4 to 97.5)	100.0 (39.8 to 100.0)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	60.0 (26.2 to 87.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec Virus at the Surface of Injection Site

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec Virus at the Surface of Injection Site

End point description:

The percentage of participants with detectable virus were evaluated from swabs of skin surface of injections. Detectable virus was defined as a positive result by TCID50.

Skin Surface of Injections Evaluable Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one swab collected from the skin surface of injections. Only participants with a positive surface of injection site qPCR test were included.

End point type	Secondary

End point timeframe:

Week 1 to Week 10

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	3	18	16
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 20.6)	0.0 (0.0 to 70.8)	0.0 (0.0 to 18.5)	0.0 (0.0 to 20.6)

End point values	Part 2: Hormone Receptor Positive Breast	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma	Part 2: Basal Cell Carcinoma (BCC)

	Cancer (HRBC)		(CSCC)	
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	11	8	4
Units: percentage of participants				
number (confidence interval 95%)	16.7 (0.4 to 64.1)	0.0 (0.0 to 28.5)	12.5 (0.3 to 52.7)	0.0 (0.0 to 60.2)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 45.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec Virus at the Exterior of the Occlusive Dressing

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec Virus at the Exterior of the Occlusive Dressing

End point description:

The percentage of participants with detectable virus were evaluated from swabs of the exterior of the occlusive dressings. Detectable virus was defined as a positive result by TCID50.

Exterior of Occlusive Dressing Evaluable Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one swab collected from the exterior of the occlusive dressing. Only participants with a positive exterior of the occlusive dressing qPCR test were included.

End point type	Secondary

End point timeframe:

Week 1 to Week 7

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	1	9	13
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 41.0)	0.0 (0.0 to 97.5)	0.0 (0.0 to 33.6)	0.0 (0.0 to 24.7)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	4	5	3
Units: percentage of participants				
number (confidence interval 95%)	16.7 (0.4 to 64.1)	0.0 (0.0 to 60.2)	0.0 (0.0 to 52.2)	0.0 (0.0 to 70.8)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec DNA at the Exterior of the Occlusive Dressing

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec DNA at the Exterior of the Occlusive Dressing

End point description:

The percentage of participants with positive qPCR and subsequent positive plaque assays were evaluated from swabs of the exterior of the occlusive dressing. Detectable DNA was defined as a positive result by qPCR analysis.

Exterior of Occlusive Dressing Evaluable Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one swab collected from the exterior of the occlusive dressing.

End point type	Secondary

End point timeframe:

Week 1 to Week 7

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	23	21
Units: percentage of participants				
number (confidence interval 95%)	30.4 (13.2 to 52.9)	20.0 (0.5 to 71.6)	39.1 (19.7 to 61.5)	61.9 (38.4 to 81.9)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	12	9	5
Units: percentage of participants				
number (confidence interval 95%)	66.7 (29.9 to 92.5)	33.3 (9.9 to 65.1)	44.4 (13.7 to 78.8)	60.0 (14.7 to 94.7)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: percentage of participants				
number (confidence interval 95%)	14.3 (0.4 to 57.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec DNA at the Oral Mucosa

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec DNA at the Oral Mucosa

End point description:

The percentage of participants with positive qPCR and subsequent positive plaque assays were evaluated from swabs of the oral mucosa. Detectable DNA was defined as a positive result by qPCR analysis.
Oral Mucosa Evaluable Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one swab collected from the oral mucosa.

End point type	Secondary

End point timeframe:

Part 1: Week 1 to Week 37. Part 2: Week 1 to Week 43

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	5	24	22
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 14.8)	0.0 (0.0 to 52.2)	29.2 (12.6 to 51.1)	4.5 (0.1 to 22.8)

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	16	10	5
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 30.8)	12.5 (1.6 to 38.3)	10.0 (0.3 to 44.5)	60.0 (14.7 to 94.7)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of participants				
number (confidence interval 95%)	10.0 (0.3 to 44.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec Virus at the Oral Mucosa

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec Virus at the Oral Mucosa

End point description:

The percentage of participants with detectable virus were evaluated from swabs of the oral mucosa. Detectable virus was defined as a positive result by TCID50.
Oral Mucosa Evaluable Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one swab collected from the oral mucosa. Only participants with a positive oral mucosa qPCR test were included.

End point type	Secondary

End point timeframe:

Week 1 to Week 7

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[29]	0[30]	7	2
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)	0.0 (0.0 to 41.0)	0.0 (0.0 to 84.2)

Notes:

[29] - No participants had a positive qPCR result.

[30] - No participants had a positive qPCR result.

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	2	3
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 97.5)	0.0 (0.0 to 84.2)	0.0 (0.0 to 84.2)	0.0 (0.0 to 70.8)

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 97.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Detectable Talimogene Laherparepvec DNA in Lesions Suspected to be Herpetic in Origin

End point title	Percentage of Participants with Detectable Talimogene Laherparepvec DNA in Lesions Suspected to be Herpetic in Origin

End point description:

The percentage of participants with positive qPCR were evaluated in any swab of a lesion suspected to be herpetic in origin. Detectable DNA was defined as a positive result by qPCR analysis.

Participants returned to the clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion was evaluated by the Investigator and swabbed if herpes simplex virus (HSV) infection was suspected.

Reactive Swab Analysis Set: Included participants who were enrolled, received at least one dose of talimogene laherparepvec, and had at least one swab sample collected from lesions that were suspected to be herpetic in origin.

End point type	Secondary

End point timeframe:

Day 1 to 30 days post-last dose of talimogene laherparepvec. The maximum duration of talimogene laherparepvec treatment was 102.4 weeks and pembrolizumab treatment was 109.3 weeks.

End point values	Part 1: Monotherapy Group A	Part 1: Monotherapy Group B	Part 1: Combination Therapy Group A	Part 1: Combination Therapy Group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	0[31]	0[32]	1
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 84.2)	(to)	(to)	100.0 (2.5 to 100.0)

Notes:

[31] - No participants had lesions suspected to be herpetic in origin.

[32] - No participants had lesions suspected to be herpetic in origin.

End point values	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[33]	0[34]	0[35]	0[36]
Units: percentage of participants				
number (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[33] - No participants had lesions suspected to be herpetic in origin.

[34] - No participants had lesions suspected to be herpetic in origin.

[35] - No participants had lesions suspected to be herpetic in origin.

[36] - No participants had lesions suspected to be herpetic in origin.

End point values	Part 2: Colorectal Adenocarcinoma (CRC)			
Subject group type	Reporting group			
Number of subjects analysed	0[37]			
Units: percentage of participants				
number (confidence interval 95%)	(to)			

Notes:

[37] - No participants had lesions suspected to be herpetic in origin.

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From the first dose date to the earlier of 90 days for treatment-emergent SAEs or 30 days for other (non-serious) TEAEs after the last dose date (talimogene laherparepvec or pembrolizumab, whichever is later) or the participants initiated new therapy.

Adverse event reporting additional description:

Median [min, max] duration of exposure was 6.1 [0.1, 33.1] weeks in Part 1 monotherapy cohorts, 9.2 [0.1, 98.3] weeks in Part 1 combination cohorts and 6.1 [0.1, 109.3] weeks in Part 2.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Part 1: Monotherapy Group B

Reporting group description:

Participants with hepatocellular carcinoma (HCC) were administered talimogene laherparepvec by intralesional injection at an initial concentration of 10^6 plaque forming unit (PFU)/mL in a volume of up to 4mL in Cohorts 1 & 2 and up to a volume of 8 mL in Cohorts 3 & 4 on Day 1 of the first 21-day cycle. The concentration of talimogene laherparepvec doses in the second and subsequent 21-day cycles were 10^7 (Cohorts 1 & 4) or 10^8 PFU/mL (Cohorts 2 & 3).

Reporting group title	Part 1: Monotherapy Group A

Reporting group description:

Participants with non-hepatocellular carcinoma (non-HCC) were administered talimogene laherparepvec by intralesional injection at an initial concentration of 10^6 plaque forming unit (PFU)/mL in a volume of up to 4mL in Cohorts 1 & 2 and up to a volume of 8 mL in Cohorts 3 & 4 on Day 1 of the first 21-day cycle. The concentration of talimogene laherparepvec doses in the second and subsequent 21-day cycles were 10^7 (Cohorts 1 & 4) or 10^8 PFU/mL (Cohorts 2 & 3)

Reporting group title	Part 1: Combination Therapy Group B

Reporting group description:

Participants with hepatocellular carcinoma (HCC) were administered talimogene laherparepvec by intralesional injection at an initial concentration of 10^6 plaque forming unit (PFU)/mL in a volume of up to 4mL in Cohorts 5, 6a (participants without viral hepatitis) and 6b (participants with well controlled viral hepatitis) on Day 1 of the first 21-day cycle. The concentration of talimogene laherparepvec doses in the second and subsequent 21-day cycles were 10^7 (Cohort 5) or 10^8 PFU/mL (Cohorts 6a and 6b). Participants were also administered 200 mg of pembrolizumab on Day 1 of each 21-day cycle as an intravenous infusion.

Reporting group title	Part 1: Combination Therapy Group A

Reporting group description:

Participants with non-hepatocellular carcinoma (non-HCC) were administered talimogene laherparepvec by intralesional injection at an initial concentration of 10^6 plaque forming unit (PFU)/mL in a volume of up to 4mL in Cohorts 5 & 6 on Day 1 of the first 21-day cycle. The concentration of talimogene laherparepvec doses in the second and subsequent 21-day cycles were 10^7 (Cohort 5) or 10^8 PFU/mL (Cohorts 6). Participants were also administered 200 mg of pembrolizumab on Day 1 of each 21-day cycle as an intravenous infusion.

Reporting group title	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)

Reporting group description:

Participants with HRBC were administered talimogene laherparepvec by intralesional injection at the maximum tolerated concentration (MTC) and maximum tolerated volume (MTV) identified in Part 1 on Day 1 of each 21-day cycle. Participants were also administered 200 mg of pembrolizumab on Day 1 of each 21-day cycle as an intravenous infusion.

Reporting group title	Part 2: Triple Negative Breast Cancer (TNBC)

Reporting group description:

Participants with TNBC were administered talimogene laherparepvec by intralesional injection at the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle. Participants were also administered 200 mg of pembrolizumab on Day 1 of each 21-day cycle as an intravenous infusion.

Reporting group title	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)

Reporting group description:

Participants with CSCC were administered talimogene laherparepvec by intralesional injection at the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle. Participants were also administered 200 mg of pembrolizumab on Day 1 of each 21-day cycle as an intravenous infusion.

Reporting group title	Part 2: Basal Cell Carcinoma (BCC)

Reporting group description:

Participants with BCC were administered talimogene laherparepvec by intralesional injection at the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle. Participants were also administered 200 mg of pembrolizumab on Day 1 of each 21-day cycle as an intravenous infusion.

Reporting group title	Part 2: Colorectal Adenocarcinoma (CRC)

Reporting group description:

Participants with CRC were administered talimogene laherparepvec by intralesional injection at the MTC and MTV identified in Part 1 on Day 1 of each 21-day cycle. Participants were also administered 200 mg of pembrolizumab on Day 1 of each 21-day cycle as an intravenous infusion.

Serious adverse events	Part 1: Monotherapy Group B	Part 1: Monotherapy Group A	Part 1: Combination Therapy Group B
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	10 / 23 (43.48%)	11 / 22 (50.00%)
number of deaths (all causes)	3	21	14
number of deaths resulting from adverse events	0	0	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver carcinoma ruptured			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	3 / 23 (13.04%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Cytokine release syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (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
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procalcitonin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (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
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (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
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Hepatic haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic cirrhosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (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
Hepatitis cholestatic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Glomerulonephritis proliferative			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
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			
Haemophilus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (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
Respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pseudomonal skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (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

Serious adverse events	Part 1: Combination Therapy Group A	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 24 (41.67%)	4 / 10 (40.00%)	7 / 18 (38.89%)

number of deaths (all causes)	22	8	13
number of deaths resulting from adverse events	0	0	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver carcinoma ruptured			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (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
Hypovolaemic shock			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (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
Hypotension			
subjects affected / exposed	0 / 24 (0.00%)	2 / 10 (20.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 24 (16.67%)	2 / 10 (20.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	5 / 5	4 / 4	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procalcitonin increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transaminases increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
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 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernial eventration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis cholestatic			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Glomerulonephritis proliferative			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (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
Acute kidney injury			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haematuria			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscular weakness			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (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
Soft tissue haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Haemophilus infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal skin infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (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
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)	Part 2: Colorectal Adenocarcinoma (CRC)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	3 / 5 (60.00%)	3 / 10 (30.00%)
number of deaths (all causes)	5	4	8
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	0 / 10 (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
Metastases to lung			

subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Liver carcinoma ruptured			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer metastatic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (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
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procalcitonin increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hernial eventration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (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
Intestinal perforation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis cholestatic			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Glomerulonephritis proliferative			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (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			
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Haemophilus infection			

subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (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
Bacterial infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (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
Soft tissue infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (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
Pseudomonal skin infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (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
Peritonitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1: Monotherapy Group B	Part 1: Monotherapy Group A	Part 1: Combination Therapy Group B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	23 / 23 (100.00%)	21 / 22 (95.45%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Tumour ulceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences (all)	0	3	2
Hypotension			
subjects affected / exposed	1 / 5 (20.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
occurrences (all)	1	1	2
Lymphoedema			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Mass excision			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
occurrences (all)	2	1	3
Application site pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
occurrences (all)	0	2	2
Axillary pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Chills			
subjects affected / exposed	1 / 5 (20.00%)	4 / 23 (17.39%)	8 / 22 (36.36%)
occurrences (all)	3	9	21
Facial pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	4 / 22 (18.18%)
occurrences (all)	0	2	5
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	3 / 22 (13.64%)
occurrences (all)	0	3	12
Injection site erythema			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site haemorrhage			
subjects affected / exposed	2 / 5 (40.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences (all)	2	1	8
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	11 / 23 (47.83%)	4 / 22 (18.18%)
occurrences (all)	1	19	5
Injection site paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Injection site ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	2 / 22 (9.09%)
occurrences (all)	1	0	3
Pyrexia			
subjects affected / exposed	4 / 5 (80.00%)	18 / 23 (78.26%)	17 / 22 (77.27%)
occurrences (all)	11	41	64
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Peripheral swelling			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Immune-mediated adverse reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hyperventilation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	3 / 5 (60.00%)	3 / 23 (13.04%)	1 / 22 (4.55%)
occurrences (all)	3	7	1
Psychiatric disorders			

Restlessness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Investigations			
Blood creatinine abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	4 / 23 (17.39%)	0 / 22 (0.00%)
occurrences (all)	1	6	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
occurrences (all)	0	5	2
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 5 (20.00%)	4 / 23 (17.39%)	0 / 22 (0.00%)
occurrences (all)	2	5	0
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	3 / 22 (13.64%)
occurrences (all)	0	1	7
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	1	2	0
Blood potassium decreased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
CD4 lymphocyte percentage decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Haemoglobin decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Creatinine renal clearance increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	1 / 5 (20.00%)	3 / 23 (13.04%)	3 / 22 (13.64%)
occurrences (all)	3	3	6
Serum ferritin decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Serum ferritin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Thyroxine free decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	3
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	3 / 22 (13.64%)
occurrences (all)	0	1	3
Injection related reaction			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Post procedural diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	2 / 5 (40.00%)	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	5	5	0
Wound haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Immunisation reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Angina pectoris			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	2 / 5 (40.00%)	3 / 23 (13.04%)	0 / 22 (0.00%)
occurrences (all)	2	4	0
Nervous system disorders			
Hypergeusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	2 / 5 (40.00%)	6 / 23 (26.09%)	2 / 22 (9.09%)
occurrences (all)	6	8	2
Facial paralysis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	2 / 22 (9.09%)
occurrences (all)	0	3	3
Lethargy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Neurotoxicity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	7 / 23 (30.43%)	3 / 22 (13.64%)
occurrences (all)	0	10	3
Iron deficiency anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Abdominal distension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	2	0	1
Abdominal pain			
subjects affected / exposed	2 / 5 (40.00%)	7 / 23 (30.43%)	8 / 22 (36.36%)
occurrences (all)	3	10	12
Abdominal pain upper			
subjects affected / exposed	2 / 5 (40.00%)	4 / 23 (17.39%)	1 / 22 (4.55%)
occurrences (all)	2	4	1
Abnormal faeces			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	5 / 23 (21.74%)	1 / 22 (4.55%)
occurrences (all)	0	5	1
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	4 / 23 (17.39%)	2 / 22 (9.09%)
occurrences (all)	0	4	3
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Dysphagia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	1 / 22 (4.55%)
occurrences (all)	0	2	1
Melaena			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 5 (40.00%)	6 / 23 (26.09%)	4 / 22 (18.18%)
occurrences (all)	4	9	7
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	5 / 23 (21.74%)	5 / 22 (22.73%)
occurrences (all)	4	8	6
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Portal vein stenosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hepatomegaly			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Liver tenderness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			

subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	1 / 5 (20.00%)	0 / 23 (0.00%)	6 / 22 (27.27%)
occurrences (all)	1	0	8
Psoriasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	2 / 22 (9.09%)
occurrences (all)	0	2	4
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	0	2	0

Chromaturia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Hypothyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Fistula			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	4 / 23 (17.39%)	1 / 22 (4.55%)
occurrences (all)	1	4	1
Arthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	4 / 22 (18.18%)
occurrences (all)	0	1	9
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	4 / 23 (17.39%)	0 / 22 (0.00%)
occurrences (all)	0	4	0
Pain in extremity			

subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Osteoporosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	0	2	0
Soft tissue infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	2 / 22 (9.09%)
occurrences (all)	0	1	2
Herpes simplex viraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Campylobacter infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0

Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	6 / 23 (26.09%)	2 / 22 (9.09%)
occurrences (all)	0	7	4
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	3 / 23 (13.04%)	1 / 22 (4.55%)
occurrences (all)	0	11	2
Hypoglycaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences (all)	0	1	1
Hypercalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	0	5
Dehydration			

subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Folate deficiency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	1 / 22 (4.55%)
occurrences (all)	0	1	2
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 23 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Part 1: Combination Therapy Group A	Part 2: Hormone Receptor Positive Breast Cancer (HRBC)	Part 2: Triple Negative Breast Cancer (TNBC)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)	10 / 10 (100.00%)	15 / 18 (83.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Tumour pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	0	1	2
Tumour ulceration			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 24 (4.17%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Hypotension			
subjects affected / exposed	6 / 24 (25.00%)	1 / 10 (10.00%)	2 / 18 (11.11%)
occurrences (all)	13	5	2
Lymphoedema			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Surgical and medical procedures			
Mass excision			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 24 (20.83%)	3 / 10 (30.00%)	5 / 18 (27.78%)
occurrences (all)	9	3	7
Application site pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Catheter site pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	13 / 24 (54.17%)	8 / 10 (80.00%)	0 / 18 (0.00%)
occurrences (all)	20	15	0
Facial pain			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	3 / 24 (12.50%)	2 / 10 (20.00%)	1 / 18 (5.56%)
occurrences (all)	5	2	1
Influenza like illness			
subjects affected / exposed	2 / 24 (8.33%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	7	2	3
Injection site erythema			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Injection site haematoma			
subjects affected / exposed	1 / 24 (4.17%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Injection site haemorrhage			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	8 / 24 (33.33%)	3 / 10 (30.00%)	1 / 18 (5.56%)
occurrences (all)	14	5	1
Injection site paraesthesia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Injection site ulcer			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Oedema			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pain			

subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	22 / 24 (91.67%)	9 / 10 (90.00%)	8 / 18 (44.44%)
occurrences (all)	73	24	19
Oedema peripheral			
subjects affected / exposed	3 / 24 (12.50%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	4	1	0
Peripheral swelling			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Immune-mediated adverse reaction			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 24 (12.50%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Dysphonia			
subjects affected / exposed	1 / 24 (4.17%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nasal congestion			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	1 / 24 (4.17%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Pulmonary embolism			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hyperventilation			

subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	2 / 24 (8.33%)	3 / 10 (30.00%)	2 / 18 (11.11%)
occurrences (all)	2	5	3
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Anxiety			
subjects affected / exposed	2 / 24 (8.33%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Investigations			
Blood creatinine abnormal			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	3 / 24 (12.50%)	3 / 10 (30.00%)	1 / 18 (5.56%)
occurrences (all)	3	5	1
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 24 (25.00%)	2 / 10 (20.00%)	1 / 18 (5.56%)
occurrences (all)	9	5	1
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 24 (12.50%)	3 / 10 (30.00%)	2 / 18 (11.11%)
occurrences (all)	4	6	2
Blood bilirubin increased			

subjects affected / exposed	3 / 24 (12.50%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	3	4	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 24 (4.17%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
CD4 lymphocyte percentage decreased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count abnormal			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 24 (4.17%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Haemoglobin decreased			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Creatinine renal clearance increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 24 (8.33%)	3 / 10 (30.00%)	0 / 18 (0.00%)
occurrences (all)	8	10	0
Neutrophil count decreased			
subjects affected / exposed	1 / 24 (4.17%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	1	10	0
Platelet count decreased			
subjects affected / exposed	1 / 24 (4.17%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	1	4	0
Serum ferritin decreased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Serum ferritin increased			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Thyroxine free decreased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Weight increased			
subjects affected / exposed	2 / 24 (8.33%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 24 (0.00%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	0	12	0
Injury, poisoning and procedural			

complications			
Fall			
subjects affected / exposed	1 / 24 (4.17%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Infusion related reaction			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Injection related reaction			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Post procedural diarrhoea			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	4	0	1
Wound haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Immunisation reaction			
subjects affected / exposed	0 / 24 (0.00%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Angina pectoris			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Tachycardia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			

Hypergeusia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	6 / 24 (25.00%)	4 / 10 (40.00%)	1 / 18 (5.56%)
occurrences (all)	10	4	1
Facial paralysis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	2 / 24 (8.33%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Lethargy			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Neurotoxicity			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Presyncope			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 24 (25.00%)	2 / 10 (20.00%)	3 / 18 (16.67%)
occurrences (all)	7	3	8
Iron deficiency anaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	4 / 24 (16.67%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Abdominal discomfort			
subjects affected / exposed	3 / 24 (12.50%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	5	0	0
Abdominal distension			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	6 / 24 (25.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	6	0	0
Abdominal pain upper			
subjects affected / exposed	6 / 24 (25.00%)	3 / 10 (30.00%)	0 / 18 (0.00%)
occurrences (all)	7	3	0
Abnormal faeces			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	4 / 24 (16.67%)	3 / 10 (30.00%)	0 / 18 (0.00%)
occurrences (all)	5	3	0
Diarrhoea			

subjects affected / exposed	5 / 24 (20.83%)	4 / 10 (40.00%)	0 / 18 (0.00%)
occurrences (all)	8	4	0
Dry mouth			
subjects affected / exposed	2 / 24 (8.33%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Dysphagia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	14 / 24 (58.33%)	7 / 10 (70.00%)	3 / 18 (16.67%)
occurrences (all)	21	13	4
Vomiting			
subjects affected / exposed	8 / 24 (33.33%)	5 / 10 (50.00%)	3 / 18 (16.67%)
occurrences (all)	9	15	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Portal vein stenosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hepatomegaly			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Liver tenderness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	6 / 24 (25.00%)	0 / 10 (0.00%)	2 / 18 (11.11%)
occurrences (all)	11	0	2
Psoriasis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	4 / 24 (16.67%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	4	1	1
Rash macular			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	1 / 24 (4.17%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	4	1	0
Skin lesion			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Renal and urinary disorders			

Pollakiuria			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Chromaturia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	2 / 18 (11.11%)
occurrences (all)	2	0	2
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Muscular weakness			
subjects affected / exposed	1 / 24 (4.17%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Limb discomfort			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Fistula			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	5 / 24 (20.83%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	8	1	4
Arthritis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Arthralgia			

subjects affected / exposed	2 / 24 (8.33%)	3 / 10 (30.00%)	2 / 18 (11.11%)
occurrences (all)	2	5	6
Myalgia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 10 (20.00%)	1 / 18 (5.56%)
occurrences (all)	1	4	3
Pain in extremity			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Osteoporosis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Diverticulitis			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Oral herpes			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Soft tissue infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	2 / 24 (8.33%)	1 / 10 (10.00%)	1 / 18 (5.56%)
occurrences (all)	2	2	1

Herpes simplex viraemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Campylobacter infection			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vaginal infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 24 (20.83%)	3 / 10 (30.00%)	1 / 18 (5.56%)
occurrences (all)	6	3	1
Hypomagnesaemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 24 (4.17%)	2 / 10 (20.00%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Hypoglycaemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			

subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Hyperglycaemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Dehydration			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Folate deficiency			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Gout			
subjects affected / exposed	0 / 24 (0.00%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Polydipsia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 24 (0.00%)	1 / 10 (10.00%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	2 / 24 (8.33%)	0 / 10 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Part 2: Cutaneous Squamous Cell Carcinoma (CSCC)	Part 2: Basal Cell Carcinoma (BCC)	Part 2: Colorectal Adenocarcinoma (CRC)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	5 / 5 (100.00%)	10 / 10 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Neoplasm			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tumour pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tumour ulceration			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Mass excision			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Application site pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Axillary pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	4	0	5
Facial pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	4 / 10 (40.00%)
occurrences (all)	2	0	6
Influenza like illness			
subjects affected / exposed	2 / 10 (20.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	3	2	0
Injection site erythema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Injection site haematoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injection site haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)	2 / 5 (40.00%)	5 / 10 (50.00%)
occurrences (all)	1	4	5
Injection site paraesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injection site ulcer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 5 (20.00%)	9 / 10 (90.00%)
occurrences (all)	4	3	18
Oedema peripheral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Immune-mediated adverse reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			

subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pulmonary embolism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hyperventilation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	1	1	1
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood creatinine abnormal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood potassium decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
CD4 lymphocyte percentage decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fibrin D dimer increased			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemoglobin decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Creatinine renal clearance increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Serum ferritin decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Serum ferritin increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Thyroxine free decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Weight increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Infusion related reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Injection related reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Post procedural diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Wound haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Immunisation reaction			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Angina pectoris			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Hypergeusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Facial paralysis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Lethargy			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neurotoxicity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 10 (10.00%)	2 / 5 (40.00%)	2 / 10 (20.00%)
occurrences (all)	3	3	2
Iron deficiency anaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Abdominal discomfort			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	5	0
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Abnormal faeces			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	0	3	1
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	7	0
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 10 (20.00%)	1 / 5 (20.00%)	4 / 10 (40.00%)
occurrences (all)	2	1	4
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Portal vein stenosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hepatomegaly			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Liver tenderness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Psoriasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	3 / 10 (30.00%)	2 / 5 (40.00%)	1 / 10 (10.00%)
occurrences (all)	6	5	1
Rash macular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			

subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Skin lesion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Chromaturia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal stiffness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Fistula			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Back pain			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Arthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	1	4	1
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
Pain in extremity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Osteoporosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Soft tissue infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	3	1	0
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	3 / 10 (30.00%)
occurrences (all)	0	0	3
Herpes simplex viraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Campylobacter infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vaginal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	3 / 10 (30.00%)
occurrences (all)	0	1	3
Hypomagnesaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			

subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Hypercalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dehydration			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Folate deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 5 (20.00%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2016	The following updates were made: • The criteria for grade 3 or higher non-hematologic laboratory values that define DLT were changed so that those that persist for > 1 week which were deemed not clinically important by both the investigator and sponsor did not trigger a DLT. Any grade 3 or higher non-hematologic laboratory value was still be considered a DLT if medical intervention was required or if it led to hospitalization. • Treatment could continue for grade 3 or higher non-hematologic laboratory values that persisted for > 1 week and were deemed not clinically important by both the investigator and sponsor so that participants could continue study treatment in spite of persistently elevated non-hematologic laboratory values with no clinical significance and long half-lives such as gamma-glutamyl transferase (GGT). • Added hepatitis D viral ribonucleic acid (RNA) as another acceptable method of testing as some institutions did not use hepatitis D serology testing. • The irRC-RECIST criteria definition was edited to make it more consistent with the conventional RECIST criteria and irRC simulating RECIST by Nishino et al. • Clarified certain laboratory tests and timing of study procedures. • Administration and editorial corrections. • Updated adverse event and disease related event language to clarify definitions and reporting periods. • Specified time points for liver tumor biopsies
18 October 2017	The following updates were made: • Added a collaborator drug, pembrolizumab, from Merck. • Aligned with more recent protocol template text. • Editorial changes (ie, typographic, grammatical, and formatting errors) and abbreviation corrections were made throughout the protocol in accordance with Amgen Inc. Style Guide.

21 October 2019	The following updates were made: • Updated study title. • Allowed intratumoral injection of talimogene laherparepvec into cutaneous, subcutaneous, and liver lesions and involved lymph nodes in Part 2 of the study. • Clarified that liver injection was not a requirement or priority in Part 2. • Expanded allowable injectable disease. • Changed the tumor types in Part 2. • Created additional BC cohort. • Created additional HCC cohort. • Allowed for well controlled viral hepatitis and allowed antiviral therapy in new cohort 6B for HCC in Part 1 and Arm VI in Part 2 of the study. • Updated study scheme. • Updated eligibility criteria. • Shortened 23 hour observation window to 6 hours in Part 2. • Added collection of PATCH 1 (PTCH) mutation status in BCC cohort if available. • Added collection of breast cancer type 1 (BRCA1) and 2 mutation status in BC cohort if available. • Added optional liver ultrasound to schedule of assessments. • Removed 24 hour and 48 hour timepoints in Week 1 and Week 4 from Part 2 schedule of assessments. • Removed assessments for anti pembrolizumab antibodies, and pembrolizumab pharmacokinetics (PK) in Part 2. • Removed blood, urine and swab collection at 24 and 48 hours in Part 2. • Allowed continuation of talimogene laherparepvec after Cycle 12 in Part 2. • Clarified maximum number of cycles. • Allowed resumption of talimogene laherparepvec at progression • Allowed up to 8 mL of talimogene laherparepvec to be used in Part 2 if 8 mL was shown safe in either Group A or B in Part 1. • Added clinical tumor assessments in Part 2. • Created a separate schedule of assessment table for Part 2. • Revised list of laboratory analytes. • Added language regarding events of clinical interest. • Added disease related events (DRE) language. • Removed language on self-evident corrections. • Updated HCC data in background and rationale sections. • Updated CTCAE version. • Updated references. • Administrative and editorial changes.
30 June 2020	The following updates were made: • Removed the 6 hour observation period and associated assessments for Part 2 participants not receiving intrahepatic injections. • Only included Part 2 enrolled participants as part of the efficacy futility analyses. • Combined arms VI and VII. • Made updates to collection time points of cytokines and qPCR. • Decreased sample size from 244 to 206. • Clarified inclusion criterion for triple negative breast cancer participants (inclusion criterion 114). • Updated administrative edits.

02 July 2021	The following updates were made: • Fixed the minor discrepancies and inconsistencies within the protocol. • Clarified medical monitor approval requirements for continuing talimogene in Part 1 and Part 2. • Updated exclusion criteria 207 to separate pneumonitis into standalone criteria 238. • Updated exclusion criteria 207 to separate pneumonitis into standalone criteria 238. • Removed the exclusion of prior checkpoint inhibitors for BCC patients to reflect the approval of cemiplimab in this population. • Updated Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab. • Updated an exception considered to continue treatment beyond progression. • updated the requirement to report fatal DREs as SAEs. • Clarified the interim safety analysis language in Part 2. • Updated SAE reporting forms. • Updated pregnancy and lactation notification forms. • Clarified primary and final analyses clinical study report (CSR) plans. • Aligned the protocol with current protocol template and safety reporting language. • Typographic, formatting and editorial changes were made.
26 October 2021	The protocol was amended to stop study-related hepatic biopsies and hepatic injections of talimogene laherparepvec based on the overall safety assessment of the hepatic hemorrhage signal following two serious adverse events of hepatic haemorrhage that resulted in death in the study. While the full safety assessment results did not suggest an increased risk of hepatic haemorrhage with talimogene laherparepvec as a medication, there was a potential risk of hepatic haemorrhage with the transcutaneous intrahepatic route of administration of talimogene laherparepvec and hepatic biopsies. As a result, the protocol is amended to remove these procedures from study conduct. Additionally, the final enrollment numbers were updated in the protocol as enrollment had stopped for this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported