Clinical trial results:
A Phase I/II Study to Assess the Safety and Efficacy of MK-3475 in Combination with Trametinib and Dabrafenib in Subjects with Advanced Melanoma

Summary

EudraCT number	2015-000681-55
Trial protocol	DK IT
Global end of trial date	14 July 2021

Results information

Result version number	v1 (current)
This version publication date	17 July 2022
First version publication date	17 July 2022

Trial information

Trial identification

Sponsor protocol code	3475-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02130466
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2021
Global end of trial reached?	Yes
Global end of trial date	14 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a 5-part dose-finding/efficacy study of pembrolizumab(Pembro)+dabrafenib(D)+trametinib(T) in participants with advanced melanoma (BRAF mutant or wild-type) and solid tumors. The parts follow: Parts (P) 1, 2 (melanoma): determined the maximum tolerated dose (MTD)/maximum administered dose (MAD) for Pembro+D+T and dose confirmation; P3 (melanoma): Pembro+D+T versus placebo+D+T; P4 (melanoma or solid tumors): determined the MTD/MAD of Pembro+T; and P5 (melanoma or solid tumors): confirmation of dose(s) in P4 and evaluated the safety/efficacy of Pembro+T. The P5 expansion cohort was not pursued with Amendment 5 (21-Mar-2019).

The primary hypotheses for P1, 2, 4, 5 were that treatment regimens were sufficiently well-tolerated to permit clinical investigation. P3 was that Pembro+D+T improved progression-free survival compared with placebo+D+T.

P1, 2 planned to explore backup combinations, if needed, of Pembro+T or Pembro+D concurrently with the Pembro+D+T arm.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2014
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	Australia: 35
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Italy: 59
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	United States: 30
Worldwide total number of subjects	184
EEA total number of subjects	73

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)	124
From 65 to 84 years	59
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

For Parts 1 and 2 of the study the optional pembrolizumab+trametinib arm was added to the study but the optional pembrolizumab+dabrafenib arm was not implemented.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Arm description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by intravenous (IV) infusion on Days 1 and 22 of each 6-week cycle (Q6W); 150 mg/day total dabrafenib orally, in a divided dose, twice a day (BID) starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally once a day (QD) starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg pembrolizumab administered by intravenous (IV) infusion on Days 1 and 22 of each 6-week cycle (Q6W) continuing up until study treatment discontinuation

Investigational medicinal product name	dabrafenib
Investigational medicinal product code	
Other name	TAFINLAR®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg/day total dabrafenib administered orally, in a divided dose, twice a day (BID) starting on Day 1 and continuing up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally once a day (QD) starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg

Arm description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W continuing up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg

Arm description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1.5 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W continuing up until study treatment discontinuation

Arm title	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Arm description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental

Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W continuing up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Investigational medicinal product name	dabrafenib
Investigational medicinal product code	
Other name	TAFINLAR®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg/day total dabrafenib administered orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg

Arm description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W continuing up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1.5 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Arm description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W continuing up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Investigational medicinal product name	dabrafenib
Investigational medicinal product code	
Other name	TAFINLAR®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg/day total dabrafenib administered orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg

Arm description:

Participants with BRAF mutant melanoma received saline placebo administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

saline placebo administered by IV infusion on Days 1 and 22 Q6W continuing up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Investigational medicinal product name	dabrafenib
Investigational medicinal product code	
Other name	TAFINLAR®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg/day total dabrafenib administered orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg

Arm description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 of each 3-week cycle (Q3W) and a concurrent dosing schedule of 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg pembrolizumab administered by IV infusion on Day 29 and continuing every 3 weeks (Q3W) up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Arm description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1.5 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg pembrolizumab administered by IV infusion on Day 15 and continuing Q3W up until study treatment discontinuation

Arm title	Part 4:4 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Arm description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg pembrolizumab administered by IV infusion on Day 29 and continuing Q3W up until study treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1.5 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Arm title	Part 4:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Arm description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally QD for 2 weeks then, starting with Week 3, an intermittent dosing schedule of 2 mg trametinib administered orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation

Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg pembrolizumab administered by IV infusion on Day 15 and continuing Q3W up until study treatment discontinuation

Arm title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg intermittent

Arm description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 1.5 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Arm type	Experimental

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1.5 mg trametinib administered orally QD for 2 weeks then, starting with Week 3, an intermittent dosing schedule of 1.5 mg trametinib administered orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation

Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg pembrolizumab administered by IV infusion on Day 15 and continuing Q3W up until study treatment discontinuation

Arm title	Part 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Arm description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1.5 mg trametinib administered orally QD starting on Day 1 and continuing up until study treatment discontinuation

Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg pembrolizumab administered by IV infusion on Day 15 and continuing Q3W up until study treatment discontinuation

Arm title	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Arm description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Arm type	Experimental
Investigational medicinal product name	pembrolizumab
Investigational medicinal product code	
Other name	MK-3475 KEYTRUDA®
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg pembrolizumab administered by IV infusion on Day 15 and continuing Q3W up until study

treatment discontinuation

Investigational medicinal product name	trametinib
Investigational medicinal product code	
Other name	MEKINIST®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg trametinib administered orally QD for 2 weeks then, starting with Week 3, an intermittent dosing schedule of 2 mg trametinib administered orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation

Number of subjects in period 1	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg
Started	7	3	2
Treated	7	3	2
Completed	0	0	0
Not completed	7	3	2
Adverse event, serious fatal	4	1	1
Consent withdrawn by subject	1	-	-
Physician decision	-	-	-
Lost to follow-up	1	-	-
Participation in Study Discontinued by Sponsor	1	2	1

Number of subjects in period 1	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Started	8	2	60
Treated	8	2	60
Completed	0	0	0
Not completed	8	2	60
Adverse event, serious fatal	3	2	30
Consent withdrawn by subject	-	-	1
Physician decision	-	-	1
Lost to follow-up	-	-	1
Participation in Study Discontinued by Sponsor	5	-	27

Number of subjects in period 1	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg
Started	60	3	4
Treated	60	3	4

Completed	0	0	0
Not completed	60	3	4
Adverse event, serious fatal	45	2	3
Consent withdrawn by subject	-	-	1
Physician decision	1	-	-
Lost to follow-up	-	-	-
Participation in Study Discontinued by Sponsor	14	1	-

Number of subjects in period 1	Part 4:4 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg	Part 4:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg intermittent
Started	5	6	3
Treated	5	6	3
Completed	0	0	0
Not completed	5	6	3
Adverse event, serious fatal	4	5	3
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
Lost to follow-up	-	-	-
Participation in Study Discontinued by Sponsor	1	1	-

Number of subjects in period 1	Part 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent
Started	12	9
Treated	12	9
Completed	0	0
Not completed	12	9
Adverse event, serious fatal	11	7
Consent withdrawn by subject	-	-
Physician decision	-	-
Lost to follow-up	1	-
Participation in Study Discontinued by Sponsor	-	2

Baseline characteristics

Reporting groups

Reporting group title	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by intravenous (IV) infusion on Days 1 and 22 of each 6-week cycle (Q6W); 150 mg/day total dabrafenib orally, in a divided dose, twice a day (BID) starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally once a day (QD) starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg

Reporting group description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg

Reporting group description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg

Reporting group description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received saline placebo administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 of each 3-week cycle (Q3W) and a concurrent dosing schedule of 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:4 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 1.5 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Reporting group title	Part 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Reporting group values	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg
Number of subjects	7	3	2
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	2	0
From 65-84 years	2	1	2
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	52.0	54.0	68.0
standard deviation	± 14.0	± 15.7	± 2.8

Sex: Female, Male Units: Participants			
Female	3	0	1
Male	4	3	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	7	3	2
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	7	3	2
Unknown or Not Reported	0	0	0
BRAF Mutation Status			
BRAF mutation testing was required for study inclusion and was done using methodology that detects both V600E and V600K mutations. Tumors that were BRAF mutation positive (V600 E or K) were eligible for treatment with pembrolizumab + trametinib + dabrafenib or trametinib + dabrafenib. Tumors that were BRAF mutation negative (wild type) were eligible for treatment with pembrolizumab + trametinib.			
Units: Subjects			
Mutant (BRAF Positive)	7	0	0
Wild Type (BRAF Negative)	0	3	2
Undetermined	0	0	0
Data Missing	0	0	0

Reporting group values	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Number of subjects	8	2	60
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	0	44
From 65-84 years	1	1	16
85 years and over	0	1	0
Age Continuous Units: years			
arithmetic mean	42.0	83.0	55.3
standard deviation	± 14.2	± 5.7	± 12.0

Sex: Female, Male Units: Participants			
Female	5	0	27
Male	3	2	33
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	8	2	60
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	7	2	57
Unknown or Not Reported	1	0	3
BRAF Mutation Status			
BRAF mutation testing was required for study inclusion and was done using methodology that detects both V600E and V600K mutations. Tumors that were BRAF mutation positive (V600 E or K) were eligible for treatment with pembrolizumab + trametinib + dabrafenib or trametinib + dabrafenib. Tumors that were BRAF mutation negative (wild type) were eligible for treatment with pembrolizumab + trametinib.			
Units: Subjects			
Mutant (BRAF Positive)	8	0	60
Wild Type (BRAF Negative)	0	2	0
Undetermined	0	0	0
Data Missing	0	0	0

Reporting group values	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg
Number of subjects	60	3	4
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	37	3	3
From 65-84 years	23	0	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57.2	47.3	50.0
standard deviation	± 14.6	± 19.9	± 18.0

Sex: Female, Male Units: Participants			
Female	24	0	2
Male	36	3	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	59	2	4
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	57	3	2
Unknown or Not Reported	2	0	2
BRAF Mutation Status			
BRAF mutation testing was required for study inclusion and was done using methodology that detects both V600E and V600K mutations. Tumors that were BRAF mutation positive (V600 E or K) were eligible for treatment with pembrolizumab + trametinib + dabrafenib or trametinib + dabrafenib. Tumors that were BRAF mutation negative (wild type) were eligible for treatment with pembrolizumab + trametinib.			
Units: Subjects			
Mutant (BRAF Positive)	60	0	0
Wild Type (BRAF Negative)	0	1	1
Undetermined	0	0	1
Data Missing	0	2	2

Reporting group values	Part 4:4 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg	Part 4:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg intermittent
Number of subjects	5	6	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	4	2
From 65-84 years	2	2	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57.0	55.5	58.0
standard deviation	± 18.0	± 17.9	± 12.2

Sex: Female, Male Units: Participants			
Female	3	5	2
Male	2	1	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	5	5	2
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	0	0
Not Hispanic or Latino	2	4	2
Unknown or Not Reported	1	2	1
BRAF Mutation Status			
BRAF mutation testing was required for study inclusion and was done using methodology that detects both V600E and V600K mutations. Tumors that were BRAF mutation positive (V600 E or K) were eligible for treatment with pembrolizumab + trametinib + dabrafenib or trametinib + dabrafenib. Tumors that were BRAF mutation negative (wild type) were eligible for treatment with pembrolizumab + trametinib.			
Units: Subjects			
Mutant (BRAF Positive)	0	0	0
Wild Type (BRAF Negative)	0	2	1
Undetermined	2	2	0
Data Missing	3	2	2

Reporting group values	Part 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent	Total
Number of subjects	12	9	184
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	7	124
From 65-84 years	5	2	59
85 years and over	0	0	1
Age Continuous Units: years			
arithmetic mean	55.7	55.9	
standard deviation	± 14.1	± 13.3	-

Sex: Female, Male Units: Participants			
Female	8	6	86
Male	4	3	98
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	11	9	179
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	3
Not Hispanic or Latino	12	9	169
Unknown or Not Reported	0	0	12
BRAF Mutation Status			
BRAF mutation testing was required for study inclusion and was done using methodology that detects both V600E and V600K mutations. Tumors that were BRAF mutation positive (V600 E or K) were eligible for treatment with pembrolizumab + trametinib + dabrafenib or trametinib + dabrafenib. Tumors that were BRAF mutation negative (wild type) were eligible for treatment with pembrolizumab + trametinib.			
Units: Subjects			
Mutant (BRAF Positive)	0	0	135
Wild Type (BRAF Negative)	5	5	22
Undetermined	6	1	12
Data Missing	1	3	15

End points

End points reporting groups

Reporting group title	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Reporting group description:	
Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by intravenous (IV) infusion on Days 1 and 22 of each 6-week cycle (Q6W); 150 mg/day total dabrafenib orally, in a divided dose, twice a day (BID) starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally once a day (QD) starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg
Reporting group description:	
Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg
Reporting group description:	
Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Reporting group description:	
Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg
Reporting group description:	
Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Reporting group description:	
Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg
Reporting group description:	
Participants with BRAF mutant melanoma received saline placebo administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg
Reporting group description:	
Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 of each 3-week cycle (Q3W) and a concurrent dosing schedule of 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg
Reporting group description:	
Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.	
Reporting group title	Part 4:4 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 1.5 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Reporting group title	Part 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Subject analysis set title	Pooled Parts 1+2:pembrolizumab+dabrafenib+1.5/2 mg trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants pooled from Parts 1 and 2 received 2 mg/kg pembrolizumab in combination with dabrafenib and 2 mg trametinib OR 2 mg/kg pembrolizumab and 1.5 or 2 mg trametinib (without dabrafenib) Q6W continuing up until study treatment discontinuation.

Subject analysis set title	Part 3: 2 mg/kg pembrolizumab+dabrafenib+trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 2 mg/kg pembrolizumab in combination with 150 mg dabrafenib and 2 mg trametinib Q6W continuing up until study treatment discontinuation.

Subject analysis set title	Part 3: placebo+dabrafenib+trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received saline placebo in combination with 150 mg dabrafenib and 2 mg trametinib Q6W continuing up until study treatment discontinuation.

Subject analysis set title	Part 4: 200 mg pembrolizumab+trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 2 mg or 1.5 mg trametinib orally QD for 2 or 4 weeks (depending on treatment regimen). Starting with Week 3 or 5 (depending on initial trametinib interval), participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent or concurrent dose schedule of trametinib orally QD continuing up until study treatment discontinuation.

Subject analysis set title	Part 5: 200 mg pembrolizumab+trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 2 mg or 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent or concurrent dose schedule of trametinib orally QD continuing up until study treatment discontinuation.

Subject analysis set title	Part 4: 200 mg pembrolizumab+2 mg trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 2 mg trametinib orally QD for 2 or 4 weeks (depending on treatment regimen). Starting with Week 3 or 5 (depending on initial trametinib interval), participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent or concurrent dose schedule of 2 mg trametinib orally QD continuing up until study treatment discontinuation.

Subject analysis set title	Part 4: 200 mg pembrolizumab+1.5 mg trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 1.5 mg trametinib orally QD for 2 or 4 weeks (depending on treatment regimen). Starting with Week 3 or 5 (depending on initial trametinib interval), participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent or concurrent dose schedule of 1.5 mg trametinib orally QD continuing up until study treatment discontinuation.

Subject analysis set title	Part 5: 200 mg pembrolizumab+2 mg trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent or concurrent dose schedule of 2 mg trametinib orally QD continuing up until study treatment discontinuation.

Subject analysis set title	Part 5: 200 mg pembrolizumab+1.5 mg trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent or concurrent dose schedule of 1.5 mg trametinib orally QD continuing up until study treatment discontinuation.

Subject analysis set title	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants pooled from Parts 1 and 2 received 2 mg/kg pembrolizumab and/or 150 mg dabrafenib and 2 mg trametinib Q6W continuing up until study treatment discontinuation.

Subject analysis set title	Pooled Parts 1+2:pembrolizumab+1.5 mg trametinib
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants pooled from Parts 1 and 2 received 2 mg/kg pembrolizumab in combination with 1.5 mg trametinib Q6W continuing up until study treatment discontinuation.

Primary: Parts 1, 2, 4, and 5: Number of Participants Who Experienced Dose-limiting Toxicities (DLTs)

End point title	Parts 1, 2, 4, and 5: Number of Participants Who Experienced Dose-limiting Toxicities (DLTs)[1][2]

End point description:

DLTs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Events were considered a DLT if occurred during the DLT evaluation period and met ≥1 of the following: significant hematologic toxicity; significant Grade ≥3 non-hematologic toxicity not previously identified or known to occur and cannot be controlled with routine supportive measures; drug-related toxicity that results in an interruption of any component of study therapy for >21 consecutive days and cannot be controlled ≤2 weeks from onset; any other Grade ≥2 non-hematological toxicity that is dose limiting with some exceptions; and liver chemistries meeting study stopping guidelines. The DLT evaluable population included all participants in Parts 1, 2, 4, and 5 who received ≥66% of planned treatments during the DLT observation period or discontinued treatment due to a DLT. Per protocol, DLT outcome analysis did not include Part 3.

End point type	Primary

End point timeframe:

Up to approximately 6 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: There was no statistical analysis planned for this endpoint.

[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: Analysis for this endpoint was prespecified to be for Parts 1, 2, 4, and 5 only. There was no statistical analysis planned for this endpoint.

End point values	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	2	8
Units: Participants	1	1	1	2

End point values	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab +Tra 2mg	Part 4:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg	Part 4:4 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: Participants	1	2	0	0

End point values	Part 4:2 weeks Tra 2mg; pembrolizumab +Tra 2mg intermittent	Part 4:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg intermittent	Part 5:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab +Tra 2mg intermittent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	12	9
Units: Participants	2	0	4	2

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Investigator in Participants Without BRAF V600 E or K Mutations

End point title	Part 2: Objective Response Rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Investigator in Participants Without BRAF V600 E

	or K Mutations[3][4]

End point description:

ORR was defined as the percentage of participants without BRAF V600 E or K mutation who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: divided into very good partial response [VGPR; >60% tumor reduction] and moderate partial response [MPR; >30-≤60% tumor reduction]) per RECIST 1.1 as assessed by investigator. The analysis population included all enrolled participants without BRAF V600 E or K mutations in Part 2. The percentage of participants who experienced a CR or PR based on RECIST 1.1 as assessed by investigator were reported.

End point type	Primary

End point timeframe:

Up to approximately 85 months

Notes:

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

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis for this endpoint was prespecified to be only for a specific population in Part 2. There was no statistical analysis planned for this endpoint.

End point values	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Percentage of Participants				
number (confidence interval 95%)	50.0 (1.3 to 98.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Part 5: ORR per RECIST 1.1 as Assessed by Investigator in Participants Without BRAF V600 E or K Mutations or With Solid Tumors Irrespective of BRAF Status

End point title	Part 5: ORR per RECIST 1.1 as Assessed by Investigator in Participants Without BRAF V600 E or K Mutations or With Solid Tumors Irrespective of BRAF Status[5][6]

End point description:

ORR was defined as the percentage of participants without BRAF V600 E or K mutation who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: divided into very good partial response [VGPR; >60% tumor reduction] and moderate partial response [MPR; >30-≤60% tumor reduction]) per RECIST 1.1 as assessed by investigator. The analysis population included all enrolled participants without BRAF V600 E or K mutations in Part 5. The percentage of participants who experienced a CR or PR based on RECIST 1.1 as assessed by investigator were reported.

End point type	Primary

End point timeframe:

Up to approximately 85 months

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis planned for this endpoint.

[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: Analysis for this endpoint was prespecified to be for Part 5 only. There was no statistical analysis planned for this endpoint.

End point values	Part 5:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab +Tra 2mg intermittent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.0 to 26.5)	33.3 (7.5 to 70.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Part 3: Progression-Free Survival (PFS) Per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations

End point title	Part 3: Progression-Free Survival (PFS) Per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations[7]

End point description:

PFS was defined as the time from randomization to the first documented disease progression (PD) or death due to any cause, whichever occurred first, based on RECIST 1.1 by investigator review. Per RECIST 1.1, PD is defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of one or more new lesions was also considered PD. PFS was analyzed using the Kaplan-Meier method and was reported in months. 9999=Upper limit for PFS not reached at time of data cut-off due to insufficient number of participants with an event. Statistical analysis used a Cox regression model with treatment as a covariate and stratified by Eastern Cooperative Oncology Group performance status and Lactate Dehydrogenase. The analysis population included all randomized participants with BRAF V600 E or K mutations in Part 3.

End point type	Primary

End point timeframe:

Up to approximately 85 months

Notes:

[7] - 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: Analysis for this endpoint was prespecified to be for Part 3 only.

End point values	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Months				
median (confidence interval 95%)	17.0 (11.3 to 9999)	9.9 (6.7 to 15.6)		

Statistical analyses

Statistical analysis title	PFS: Pembrolizumab versus Placebo
Statistical analysis description:	
Cox regression model	
Comparison groups	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg v Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.74

Primary: Parts 1, 2, 4, and 5: Number of Participants Who Experienced an Adverse Event (AE)

End point title	Parts 1, 2, 4, and 5: Number of Participants Who Experienced an Adverse Event (AE)[8][9]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE was any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the study drug, was also an AE. The analysis population included all participants who received at least one dose of study treatment in Parts 1, 2, 4, and 5. The number of participants who experienced an AE was reported. Per protocol, AE outcome analysis did not include Part 3.

End point type	Primary

End point timeframe:

Up to approximately 32 months

Notes:

[8] - 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: There was no statistical analysis planned for this endpoint.

[9] - 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: Analysis for this endpoint was prespecified to be for Parts 1, 2, 4, and 5 only. There was no statistical analysis planned for this endpoint.

End point values	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	2	8
Units: Participants	7	3	2	8

End point values	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab +Tra 2mg	Part 4:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg	Part 4:4 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: Participants	2	3	4	5

End point values	Part 4:2 weeks Tra 2mg; pembrolizumab +Tra 2mg intermittent	Part 4:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg intermittent	Part 5:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab +Tra 2mg intermittent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	12	9
Units: Participants	6	3	11	9

Statistical analyses

No statistical analyses for this end point

Primary: Parts 1, 2, 4, and 5: Number of Participants Who Discontinued Study Treatment Due to an AE

End point title	Parts 1, 2, 4, and 5: Number of Participants Who Discontinued Study Treatment Due to an AE[10][11]

End point description:

An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily had to have a causal relationship with this treatment. An AE was any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening of a pre-existing condition that was temporally associated with the use of the study drug, was also an AE. The analysis population included all participants who received at least one dose of study treatment in Parts 1, 2, 4, and 5. The number of participants who discontinued study treatment due to an AE was reported. Per protocol, discontinuation outcome analysis did not include Part 3.

End point type	Primary

End point timeframe:

Up to approximately 29 months

Notes:

[10] - 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: There was no statistical analysis planned for this endpoint.

[11] - 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: Analysis for this endpoint was prespecified to be for Parts 1, 2, 4, and 5 only. There was no statistical analysis planned for this endpoint.

End point values	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	3	2	8
Units: Participants	2	2	1	5

End point values	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab +Tra 2mg	Part 4:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg	Part 4:4 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	4	5
Units: Participants	2	1	0	4

End point values	Part 4:2 weeks Tra 2mg; pembrolizumab +Tra 2mg intermittent	Part 4:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg intermittent	Part 5:2 weeks Tra 1.5mg; pembrolizumab +Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab +Tra 2mg intermittent
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	12	9
Units: Participants	2	1	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: ORR per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations

End point title	Part 1: ORR per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations[12]

End point description:

ORR was defined as the percentage of participants who had a CR (Disappearance of all target lesions) or a PR (divided into very good partial response [VGPR; >60% tumor reduction] and moderate partial response [MPR; >30-≤60% tumor reduction]) per RECIST 1.1 as assessed by investigator. The analysis

population included all enrolled participants with BRAF V600 E or K mutations in Part 1. The percentage of participants who experienced a CR or PR as assessed by the investigator was presented.

End point type	Secondary

End point timeframe:

Up to approximately 85 months

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis for this endpoint was prespecified to be only for a specific population in Part 1. There was no statistical analysis planned for this endpoint.

End point values	Part 1:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Percentage of participants				
number (confidence interval 95%)	57.1 (18.4 to 90.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: ORR per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations

End point title	Part 2: ORR per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations[13]

End point description:

ORR was defined as the percentage of participants who had a CR (Disappearance of all target lesions) or a PR (divided into very good partial response [VGPR; >60% tumor reduction] and moderate partial response [MPR; >30-≤60% tumor reduction]) per RECIST 1.1 as assessed by investigator. The analysis population included all enrolled participants with BRAF V600 E or K mutations in Part 2. The percentage of participants who experienced a CR or PR as assessed by the investigator was presented.

End point type	Secondary

End point timeframe:

Up to approximately 85 months

Notes:

[13] - 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: Analysis for this endpoint was prespecified to be only for a specific population in Part 2. There was no statistical analysis planned for this endpoint.

End point values	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg			

Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage of Participants				
number (confidence interval 95%)	75.0 (34.9 to 96.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 3: ORR per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations

End point title	Part 3: ORR per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations[14]

End point description:

ORR was defined as the percentage of participants who had a CR (Disappearance of all target lesions) or a PR (divided into very good partial response [VGPR; >60% tumor reduction] and moderate partial response [MPR; >30-≤60% tumor reduction]) per RECIST 1.1 as assessed by investigator. The analysis population included all randomized participants with BRAF V600 E or K mutations in Part 3. The percentage of participants who experienced a CR or PR as assessed by the investigator was presented.

End point type	Secondary

End point timeframe:

Up to approximately 85 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis for this endpoint was prespecified to be for Part 3 only. There was no statistical analysis planned for this endpoint.

End point values	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Percentage of Participants				
number (confidence interval 95%)	65.0 (51.6 to 76.9)	71.7 (58.6 to 82.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 3: Duration of Response (DOR) per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations

End point title	Part 3: Duration of Response (DOR) per RECIST 1.1 as Assessed by Investigator in Participants With BRAF V600 E or K Mutations[15]

End point description:

For participants who demonstrated a confirmed CR (Disappearance of all target lesions) or a confirmed PR (divided by VGPR [>60% tumor reduction] and MPR [>30-≤60% tumor reduction]) per RECIST 1.1 as assessed by the investigator, DOR was defined as the time from first documented evidence of CR or PR until progressive disease (PD). Per RECIST 1.1, PD was defined as at least a 20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered PD. The analysis population included all randomized participants with BRAF V600 E or K mutations who had a confirmed CR or PR in Part 3. The DOR as assessed by the investigator was analyzed using Kaplan-Meier method and reported in months. 9999=Upper limit for DOR was not reached at time of data cut-off due to insufficient number of responding participants with relapse.

End point type	Secondary

End point timeframe:

Up to approximately 85 months

Notes:

[15] - 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: Analysis for this endpoint was prespecified to be for Part 3 only. There was no statistical analysis planned for this endpoint.

End point values	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	43		
Units: Months				
median (confidence interval 95%)	30.2 (14.1 to 9999)	12.1 (6.0 to 15.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 3: Overall Survival (OS) in Participants With BRAF V600 E or K Mutations

End point title	Part 3: Overall Survival (OS) in Participants With BRAF V600 E or K Mutations[16]

End point description:

OS was defined as the time from randomization to death due to any cause. OS was analyzed using the Kaplan-Meier method and was reported in months. Statistical analysis used a Cox regression model with treatment as a covariate and stratified by Eastern Cooperative Oncology Group performance status and Lactate Dehydrogenase. The analysis population included all randomized participants with BRAF V600 E or K mutations in Part 3. 9999=Upper limit for OS was not reached at time of data cut-off due to insufficient number of participants with an event.

End point type	Secondary

End point timeframe:

Up to approximately 85 months

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Analysis for this endpoint was prespecified to be for Part 3 only.

End point values	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	60		
Units: Months				
median (confidence interval 95%)	46.3 (23.9 to 9999)	26.3 (18.2 to 38.6)		

Statistical analyses

Statistical analysis title	OS: Pembrolizumab versus Placebo
Statistical analysis description: Cox regression model	
Comparison groups	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg v Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.95

Secondary: Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point title	Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point description:

Cmax was defined as the maximum concentration of pembrolizumab observed after administration of 2 mg/kg pembrolizumab in combination with dabrafenib and/or trametinib. Blood samples were collected at multiple time points to estimate the Cmax of pembrolizumab. All participants who received pembrolizumab from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 2 mg/kg pembrolizumab and who had available data for the analysis of Cmax. The Cmax of pembrolizumab is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: predose, postdose, 24 - 96 hours (hrs) postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+dabrafenib+1.5/2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: µg/mL				
arithmetic mean (standard deviation)	52.3 (± 9.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point title	Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point description:

Cmax was defined as the maximum concentration of pembrolizumab observed after administration of 2 mg/kg pembrolizumab in combination with dabrafenib and trametinib. Blood samples were collected at multiple time points to estimate the Cmax of pembrolizumab. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 2 mg/kg pembrolizumab and who had available data for the analysis of Cmax. The Cmax of pembrolizumab is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: µg/mL				
arithmetic mean (standard deviation)	48.9 (± 11.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point title	Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point description:

Cmax was defined as the maximum concentration of pembrolizumab observed after administration of 200 mg pembrolizumab in combination with trametinib. Blood samples were collected at multiple time points to estimate the Cmax of pembrolizumab. The analysis population consisted of all participants from Part 4 who received ≥1 dose of 200 mg pembrolizumab and who had available data for the analysis of Cmax. The Cmax of pembrolizumab is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: µg/mL				
arithmetic mean (standard deviation)	77.8 (± 16.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5

End point title	Maximum Concentration (Cmax) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5

End point description:

Cmax was defined as the maximum concentration of pembrolizumab observed after administration of 200 mg pembrolizumab in combination with trametinib. Blood samples were collected at multiple time points to estimate the Cmax of pembrolizumab. The analysis population consisted of all participants from Part 5 who received ≥1 dose of 200 mg pembrolizumab and who had available data for the analysis of Cmax.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 5: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[17]			
Units: µg/mL				
arithmetic mean (standard deviation)	()			

Notes:

[17] - There were no participants with data available for the analysis of the Cmax of pembrolizumab.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point title	Trough Concentration (Ctrough) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point description:

Ctrough was defined as the lowest concentration of pembrolizumab that occurred immediately prior to the next dose of 2 mg/kg pembrolizumab administered in combination with dabrafenib and/or trametinib. Blood samples were collected at multiple time points to estimate the Ctrough of pembrolizumab. All participants who received pembrolizumab from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 2 mg/kg pembrolizumab and who had available data for the analysis of Ctrough. The Ctrough of pembrolizumab is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+dabrafenib+1.5/2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: µg/mL				
arithmetic mean (standard deviation)	11.2 (± 2.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Pembrolizumab Following

Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point title	Trough Concentration (Ctrough) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point description:

Ctrough was defined as the lowest concentration of pembrolizumab that occurred immediately prior to the next dose of 2 mg/kg pembrolizumab administered in combination with dabrafenib and trametinib. Blood samples were collected at multiple time points to estimate the Ctrough of pembrolizumab. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 2 mg/kg pembrolizumab and who had available data for the analysis of Ctrough. The Ctrough of pembrolizumab is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab +dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: µg/mL				
arithmetic mean (standard deviation)	10.6 (± 3.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point title	Trough Concentration (Ctrough) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point description:

Ctrough was defined as the lowest concentration of pembrolizumab that occurred immediately prior to the next dose of 200 mg pembrolizumab administered in combination with trametinib. Blood samples were collected at multiple time points to estimate the Ctrough of pembrolizumab. The analysis population consisted of all participants from Part 4 who received ≥1 dose of 200 mg pembrolizumab and who had available data for the analysis of Ctrough. The Ctrough of pembrolizumab is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: µg/mL				
arithmetic mean (standard deviation)	17.0 (± 7.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5

End point title	Trough Concentration (Ctrough) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5

End point description:

Ctrough was defined as the lowest concentration of pembrolizumab that occurred immediately prior to the next dose of 200 mg pembrolizumab administered in combination with trametinib. Blood samples were collected at multiple time points to estimate the Ctrough of pembrolizumab. The analysis population consisted of all participants from Part 5 who received ≥1 dose of 200 mg pembrolizumab and who had available data for the analysis of Ctrough. The Ctrough of pembrolizumab is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 5: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[18]			
Units: µg/mL				
arithmetic mean (standard deviation)	()			

Notes:

[18] - There were no participants with data available for the analysis of the Ctrough of pembrolizumab.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants Pooled From Parts 1 and 2

End point title	Maximum Concentration (Cmax) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants Pooled From Parts 1 and 2

End point description:

Cmax was defined as the maximum concentration of dabrafenib observed after administration of 150 mg dabrafenib in combination with 2 mg/kg pembrolizumab and 2 mg trametinib. Blood samples were collected at multiple time points to estimate the Cmax of dabrafenib. All participants who received dabrafenib from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 150 mg dabrafenib and who had available data for the analysis of Cmax. The Cmax of dabrafenib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: ng/mL				
arithmetic mean (standard deviation)	683 (± 905)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point title	Maximum Concentration (Cmax) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point description:

Cmax was defined as the maximum concentration of dabrafenib observed after administration of 150 mg dabrafenib in combination with 2 mg/kg pembrolizumab and 2 mg trametinib. Blood samples were collected at multiple time points to estimate the Cmax of dabrafenib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 150 mg dabrafenib and pembrolizumab and who had available data for the analysis of Cmax. The Cmax of dabrafenib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab +dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	53			
Units: ng/mL				
arithmetic mean (standard deviation)	643 (± 643)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point title	Maximum Concentration (Cmax) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point description:

Cmax was defined as the maximum concentration of dabrafenib observed after administration of 150 mg dabrafenib in combination with saline placebo and 2 mg trametinib. Blood samples were collected at multiple time points to estimate the Cmax of dabrafenib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 150 mg dabrafenib and placebo and who had available data for the analysis of Cmax. The Cmax of dabrafenib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: ng/mL				
arithmetic mean (standard deviation)	642 (± 829)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants Pooled From Parts 1 and 2

End point title	Trough Concentration (Ctrough) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants

	Pooled From Parts 1 and 2

End point description:

Ctrough was defined as the lowest concentration of dabrafenib that occurred immediately prior to the next dose of 150 mg dabrafenib administered in combination with 2 mg/kg pembrolizumab and 2 mg trametinib. Blood samples were collected at multiple time points to estimate the Ctrough of dabrafenib. All participants who received dabrafenib from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 150 mg dabrafenib and who had available data for the analysis of Ctrough. The Ctrough of dabrafenib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)	156 (± 367)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point title	Trough Concentration (Ctrough) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point description:

Ctrough was defined as the lowest concentration of dabrafenib that occurred immediately prior to the next dose of 150 mg dabrafenib administered in combination with 2 mg/kg pembrolizumab and 2 mg trametinib. Blood samples were collected at multiple time points to estimate the Ctrough of dabrafenib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 150 mg dabrafenib and pembrolizumab and who had available data for the analysis of Ctrough. The Ctrough of dabrafenib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab +dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: ng/mL				
arithmetic mean (standard deviation)	103 (± 204)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point title	Trough Concentration (Ctrough) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point description:

Ctrough was defined as the lowest concentration of dabrafenib that occurred immediately prior to the next dose of 150 mg dabrafenib administered in combination with saline placebo and 2 mg trametinib. Blood samples were collected at multiple time points to estimate the Ctrough of dabrafenib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 150 mg dabrafenib and placebo and who had available data for the analysis of Ctrough. The Ctrough of dabrafenib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: ng/mL				
arithmetic mean (standard deviation)	183 (± 384)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants Pooled From Parts 1 and 2

End point title	Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants

	Pooled From Parts 1 and 2

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 2 mg trametinib in combination with 2 mg/kg pembrolizumab and 150 mg dabrafenib. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. All participants who received 2 mg trametinib from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 2 mg trametinib and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: ng/mL				
arithmetic mean (standard deviation)	19.3 (± 8.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2

End point title	Maximum Concentration (Cmax) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 1.5 mg trametinib in combination with 2 mg/kg pembrolizumab. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. All participants who received 1.5 mg trametinib from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 1.5 mg trametinib and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: ng/mL				
arithmetic mean (standard deviation)	30.3 (± 17.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point title	Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 2 mg trametinib in combination with 2 mg/kg pembrolizumab and 150 mg dabrafenib. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 2 mg trametinib and pembrolizumab and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: ng/mL				
arithmetic mean (standard deviation)	16.3 (± 6.80)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point title	Maximum Concentration (Cmax) of Trametinib Following

	Administration of 2 mg Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 2 mg trametinib in combination with saline placebo and 150 mg dabrafenib. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 2 mg trametinib and placebo and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	53			
Units: ng/mL				
arithmetic mean (standard deviation)	16.2 (± 6.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 2 mg trametinib in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. The analysis population consisted of all participants from Part 4 who received ≥1 dose of 2 mg trametinib and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: ng/mL				
arithmetic mean (standard deviation)	18.5 (± 12.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Maximum Concentration (Cmax) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 1.5 mg trametinib in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. The analysis population consisted of all participants from Part 4 who received ≥1 dose of 1.5 mg trametinib and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
arithmetic mean (standard deviation)	16.7 (± 7.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Maximum Concentration (Cmax) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 2 mg trametinib in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. The analysis population consisted of all participants from Part 5 who received ≥1 dose of 2 mg trametinib and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 5: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: ng/mL				
arithmetic mean (standard deviation)	7.54 (± 8.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Maximum Concentration (Cmax) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point description:

Cmax was defined as the maximum concentration of trametinib observed after administration of 1.5 mg trametinib in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Cmax of trametinib. The analysis population consisted of all participants from Part 5 who received ≥1 dose of 1.5 mg trametinib and who had available data for the analysis of Cmax. The Cmax of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 5: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: ng/mL				
arithmetic mean (standard deviation)	14.3 (± 7.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants Pooled From Parts 1 and 2

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants Pooled From Parts 1 and 2

End point description:

Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 2 mg trametinib administered in combination with 2 mg/kg pembrolizumab and 150 mg dabrafenib. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. All participants who received 2 mg trametinib from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 2 mg trametinib and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)	13.7 (± 9.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2

End point description:

Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 1.5 mg trametinib administered in combination with 2 mg/kg pembrolizumab. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. All participants who received 1.5 mg trametinib from Parts 1 and 2 were treated as a single arm and analyzed as a single study population for this outcome measure since Part 2 was the dose confirmation phase of Part 1. The analysis population consisted of all participants pooled from Parts 1 and 2 who received ≥1 dose of 1.5 mg trametinib and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: ng/mL				
arithmetic mean (standard deviation)	20.5 (± 9.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point description:

Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 2 mg trametinib administered in combination with 2 mg/kg pembrolizumab and 150 mg dabrafenib. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 2 mg trametinib and pembrolizumab and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	54			
Units: ng/mL				
arithmetic mean (standard deviation)	9.93 (± 5.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point description:

Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 2 mg trametinib administered in combination with saline placebo and 150 mg dabrafenib. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. The analysis population consisted of all participants from Part 3 who received ≥1 dose of 2 mg trametinib and placebo and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	58			
Units: ng/mL				
arithmetic mean (standard deviation)	10.7 (± 5.14)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 2 mg trametinib administered in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. The analysis population consisted of all participants from Part 4 who received ≥1 dose of 2 mg trametinib and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	6			
Units: ng/mL				
arithmetic mean (standard deviation)	12.3 (± 9.45)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 1.5 mg trametinib administered in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. The analysis population consisted of all participants from Part 4 who received ≥1 dose of 1.5 mg trametinib and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: ng/mL				
arithmetic mean (standard deviation)	8.64 (± 5.65)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point description:	
Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 2 mg trametinib administered in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. The analysis population consisted of all participants from Part 5 who received ≥1 dose of 2 mg trametinib and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.	

End point values	Part 5: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: ng/mL				
arithmetic mean (standard deviation)	6.69 (± 5.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Ctrough) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Trough Concentration (Ctrough) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5
End point description:	
Ctrough was defined as the lowest concentration of trametinib that occurred immediately prior to the next dose of 1.5 mg trametinib administered in combination with 200 mg pembrolizumab. Blood samples were collected at multiple time points to estimate the Ctrough of trametinib. The analysis population consisted of all participants from Part 5 who received ≥1 dose of 1.5 mg trametinib and who had available data for the analysis of Ctrough. The Ctrough of trametinib is presented.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.	

End point values	Part 5: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: ng/mL				
arithmetic mean (standard deviation)	10.6 (± 6.79)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point title	Clearance (Cl) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of pembrolizumab, defined as the volume of plasma from which pembrolizumab is eliminated per unit time following pembrolizumab administration. As specified by the protocol, the Cl of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+dabrafenib+1.5/2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[19]			
Units: Liters/hour (L/hr)				
geometric mean (geometric coefficient of variation)	()			

Notes:

[19] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point title	Clearance (Cl) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point description:	
Blood samples were to be collected at pre-specified time points for analysis of the Cl of pembrolizumab, defined as the volume of plasma from which pembrolizumab is eliminated per unit time following pembrolizumab administration. As specified by the protocol, the Cl of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 1: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.	

End point values	Part 3: 2 mg/kg pembrolizumab +dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[20]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[20] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5

End point title	Clearance (Cl) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5
End point description:	
Blood samples were to be collected at pre-specified time points for analysis of the Cl of pembrolizumab, defined as the volume of plasma from which pembrolizumab is eliminated per unit time following pembrolizumab administration. As specified by the protocol, the Cl of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.	

End point values	Part 5: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[21]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[21] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point title	Clearance (Cl) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of pembrolizumab, defined as the volume of plasma from which pembrolizumab is eliminated per unit time following pembrolizumab administration. As specified by the protocol, the Cl of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[22]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[22] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants Pooled From Parts 1 and 2

End point title	Clearance (Cl) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of dabrafenib, defined as the volume of plasma from which dabrafenib is eliminated per unit time following dabrafenib administration. As specified by the protocol, the Cl of dabrafenib was only to be analyzed if required and no data were collected since, by the time of final analysis, dabrafenib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of dabrafenib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[23]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[23] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point title	Clearance (Cl) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of dabrafenib, defined as the volume of plasma from which dabrafenib is eliminated per unit time following dabrafenib administration. As specified by the protocol, the Cl of dabrafenib was only to be analyzed if required and no data were collected since, by the time of final analysis, dabrafenib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of dabrafenib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab +dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[24]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[24] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point title	Clearance (Cl) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of dabrafenib, defined as the volume of plasma from which dabrafenib is eliminated per unit time following dabrafenib administration. As specified by the protocol, the Cl of dabrafenib was only to be analyzed if required and no data were collected since, by the time of final analysis, dabrafenib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of dabrafenib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[25]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[25] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2

End point title	Clearance (Cl) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[26]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[26] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants Pooled From Parts 1 and 2

End point title	Clearance (Cl) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[27]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[27] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point title	Clearance (Cl) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[28]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[28] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 2 mg

Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point title	Clearance (Cl) of Trametinib Following Administration of 2 mg Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[29]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[29] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Clearance (Cl) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[30]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[30] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Clearance (Cl) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[31]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[31] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Clearance (Cl) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point description:	
Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.	

End point values	Part 5: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[32]			
Units: L/hr				
geometric mean (geometric coefficient of variation)	()			

Notes:

[32] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (Cl) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Clearance (Cl) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5
End point description:	
Blood samples were to be collected at pre-specified time points for analysis of the Cl of trametinib, defined as the volume of plasma from which trametinib is eliminated per unit time following trametinib administration. As specified by the protocol, the Cl of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.	
End point type	Secondary
End point timeframe:	
Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.	

End point values	Part 5: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[33]			
Units: L/hr				
geometric mean (geometric coefficient	()			

of variation)

Notes:

[33] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point title	Volume of Distribution (Vc) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and/or Trametinib in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of pembrolizumab, defined as the theoretical volume that would be necessary to contain the total amount of administered pembrolizumab at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+dabrafenib+1.5/2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[34]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[34] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point title	Volume of Distribution (Vc) of Pembrolizumab Following Administration of 2 mg/kg Pembrolizumab in Combination with Dabrafenib and Trametinib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of pembrolizumab, defined as the theoretical volume that would be necessary to contain the total amount of administered pembrolizumab at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 22: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab +dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[35]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[35] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point title	Volume of Distribution (Vc) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 4

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of pembrolizumab, defined as the theoretical volume that would be necessary to contain the total amount of administered pembrolizumab at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[36]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[36] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5

End point title	Volume of Distribution (Vc) of Pembrolizumab Following Administration of 200 mg Pembrolizumab in Combination with Trametinib in Participants From Part 5

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of pembrolizumab, defined as the theoretical volume that would be necessary to contain the total amount of administered pembrolizumab at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of pembrolizumab was only to be analyzed if required and no data were collected since, by the time of final analysis, pembrolizumab pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of pembrolizumab characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15: predose, postdose, 24 - 96 hrs postdose; Cycle 1 Day 36: predose, postdose; Cycle 2 Day 1: predose, postdose. Each cycle is a 21-day cycle.

End point values	Part 5: 200 mg pembrolizumab +trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[37]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[37] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants Pooled From Parts 1 and 2

End point title	Volume of Distribution (Vc) of Dabrafenib Following

	Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of dabrafenib, defined as the theoretical volume that would be necessary to contain the total amount of administered dabrafenib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of dabrafenib was only to be analyzed if required and no data were collected since, by the time of final analysis, dabrafenib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of dabrafenib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[38]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[38] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point title	Volume of Distribution (Vc) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with 2 mg/kg Pembrolizumab and 2 mg Trametinib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of dabrafenib, defined as the theoretical volume that would be necessary to contain the total amount of administered dabrafenib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of dabrafenib was only to be analyzed if required and no data were collected since, by the time of final analysis, dabrafenib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of dabrafenib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab +dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[39]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[39] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point title	Volume of Distribution (Vc) of Dabrafenib Following Administration of 150 mg Dabrafenib in Combination with Placebo and 2 mg Trametinib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of dabrafenib, defined as the theoretical volume that would be necessary to contain the total amount of administered dabrafenib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of dabrafenib was only to be analyzed if required and no data were collected since, by the time of final analysis, dabrafenib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of dabrafenib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[40]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[40] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg

Dabrafenib in Participants Pooled From Parts 1 and 2	
End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts1+2:pembrolizumab and/or dabrafenib+2mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[41]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[41] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2	
End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 2 mg/kg Pembrolizumab in Participants Pooled From Parts 1 and 2

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Pooled Parts 1+2:pembrolizumab+1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[42]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[42] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with 2 mg/kg Pembrolizumab and 150 mg Dabrafenib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: 2 mg/kg pembrolizumab+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[43]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[43] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with Placebo and 150 mg Dabrafenib in Participants From Part 3

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 22: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 3: placebo+dabrafenib+trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[44]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[44] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[45]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[45] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 1.5 mg Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 4

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 4: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[46]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[46] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 2 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 5: 200 mg pembrolizumab +2 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[47]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[47] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vc) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point title	Volume of Distribution (Vc) of Trametinib Following Administration of 1.5 mg of Trametinib in Combination with 200 mg Pembrolizumab in Participants From Part 5

End point description:

Blood samples were to be collected at pre-specified time points for analysis of the Vc of trametinib, defined as the theoretical volume that would be necessary to contain the total amount of administered trametinib at the same concentration that it is observed in the blood plasma. As specified by the protocol, the Vc of trametinib was only to be analyzed if required and no data were collected since, by the time of final analysis, trametinib pharmacokinetics (PK) in melanoma participants had been well characterized and found to be consistent with the overall clinical pharmacology of trametinib characterized across indications.

End point type	Secondary

End point timeframe:

Cycle 1 Day 36: predose, postdose, 4 - 6 hrs postdose. Each cycle is a 21-day cycle.

End point values	Part 5: 200 mg pembrolizumab +1.5 mg trametinib			
Subject group type	Subject analysis set			
Number of subjects analysed	0[48]			
Units: Liters				
geometric mean (geometric coefficient of variation)	()			

Notes:

[48] - The analysis was not performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 85 months

Adverse event reporting additional description:

All-cause mortality=all randomized participants and AEs=all participants who received ≥1 dose of treatment. Per protocol, disease progression (DP) was not considered an AE unless related to treatment. Medical Dictionary for Regulatory Activities (MedDRA) terms neoplasm progression (NP), malignant NP, and DP not related to treatment were excluded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Part 1:pembrolizumab 2 mg/kg+dabrafenib150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by intravenous (IV) infusion on Days 1 and 22 of each 6-week cycle (Q6W); 150 mg/day total dabrafenib orally, in a divided dose, twice a day (BID) starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally once a day (QD) starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg

Reporting group description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg

Reporting group description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg

Reporting group description:

Participants with BRAF wild-type melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W and 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received 2 mg/kg pembrolizumab administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg

Reporting group description:

Participants with BRAF mutant melanoma received saline placebo administered by IV infusion on Days 1 and 22 Q6W; 150 mg/day total dabrafenib orally, in a divided dose, BID starting on Day 1 and continuing up until study treatment discontinuation; and 2 mg trametinib orally QD starting on Day 1

and continuing up until study treatment discontinuation.

Reporting group title	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 2 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:4 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 4 weeks. Starting with Week 5, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Reporting group title	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 1.5 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Reporting group title	Part 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 1.5 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and a concurrent dosing schedule of 1.5 mg trametinib orally QD starting on Day 1 and continuing up until study treatment discontinuation.

Reporting group title	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent

Reporting group description:

Participants with BRAF wild-type melanoma or solid tumors (irrespective of BRAF status) received 2 mg trametinib orally QD for 2 weeks. Starting with Week 3, participants received 200 mg pembrolizumab administered by IV infusion on Day 1 Q3W and an intermittent dose schedule of 2 mg trametinib orally QD with 1 week OFF trametinib and 2 weeks ON trametinib continuing up until study treatment discontinuation.

Serious adverse events	Part 1:pembrolizumab 2 mg/kg+dabrafenib150 mg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	1 / 2 (50.00%)
number of deaths (all causes)	4	1	1
number of deaths resulting from	0	0	0

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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 angiosarcoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Arterial thrombosis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Chills			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Amylase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Acute motor axonal neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uveitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Discoloured vomit			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faeces discoloured			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Cholecystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Drug-induced liver injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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 sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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 bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-ovarian abscess			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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			
Diabetes mellitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
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:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	1 / 2 (50.00%)	36 / 60 (60.00%)
number of deaths (all causes)	3	2	31
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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 angiosarcoma			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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			
Arterial thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	8 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	6 / 60 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
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			
Atrial fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	0 / 60 (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
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Acute motor axonal neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (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			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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			
Colitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Discoloured vomit			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Faeces discoloured			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (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
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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 impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-ovarian abscess			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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			
Diabetes mellitus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
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 3:placebo+dabrafenib 150 mg+trametinib 2 mg	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 60 (33.33%)	1 / 3 (33.33%)	1 / 4 (25.00%)
number of deaths (all causes)	45	2	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Breast cancer			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Skin angiosarcoma			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Mucosal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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	8 / 60 (13.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	7 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Pneumomediastinum			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Pulmonary embolism			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood creatinine increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Mitral valve incompetence			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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			
Acute motor axonal neuropathy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Brain oedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Haemorrhagic stroke			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Febrile neutropenia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Neutropenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (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
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Uveitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Discoloured vomit			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faeces discoloured			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip swelling			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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			
Cholecystitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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			

Eczema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Rash erythematous			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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 impairment			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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			
Muscular weakness			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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 sepsis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 3 (33.33%)	0 / 4 (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
Gastroenteritis viral			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Infection			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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 bacterial			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-ovarian abscess			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (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
Hypocalcaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
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 4:4 weeks Tra	Part 4:2 weeks Tra	Part 4:2 weeks Tra

	1.5mg; pembrolizumab+Tra 1.5mg	2mg; pembrolizumab+Tra 2mg intermittent	1.5mg; pembrolizumab+Tra 1.5mg intermittent
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	4 / 6 (66.67%)	1 / 3 (33.33%)
number of deaths (all causes)	4	5	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 angiosarcoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			
Arterial thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 / 6 (0.00%)	0 / 3 (0.00%)
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			
Chills			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mucosal haemorrhage			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Pneumonitis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Amylase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			
Acute motor axonal neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Retinal detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Discoloured vomit			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Faeces discoloured			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			

Cholecystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 impairment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tubulointerstitial nephritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 sepsis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (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
Cellulitis			

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (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
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Parotitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 bacterial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia chlamydial			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (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
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubo-ovarian abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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			
Diabetes mellitus			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
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 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	2 / 9 (22.22%)	
number of deaths (all causes)	11	7	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angiosarcoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin angiosarcoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar hypertrophy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lipase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acute motor axonal neuropathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discoloured vomit			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dysphagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces discoloured			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia chlamydial			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			

subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubo-ovarian abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1:pembrolizumab 2 mg/kg+dabrafenib150 mg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 2 mg	Part 1:pembrolizumab 2 mg/kg+trametinib 1.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	3 / 3 (100.00%)	2 / 2 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Basal cell carcinoma			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	1 / 2 (50.00%)
occurrences (all)	0	2	1
Cancer pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Flushing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypertensive crisis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	1 / 2 (50.00%)
occurrences (all)	2	1	1
Lymphoedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Phlebitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 7 (42.86%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Axillary pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Catheter site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	6 / 7 (85.71%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	21	2	0
Face oedema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Facial pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	4 / 7 (57.14%)	1 / 3 (33.33%)	2 / 2 (100.00%)
occurrences (all)	5	1	2
Feeling abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Feeling cold			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Generalised oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	2 / 7 (28.57%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	2	2	0
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Medical device site rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 7 (0.00%)	3 / 3 (100.00%)	0 / 2 (0.00%)
occurrences (all)	0	8	0
Pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Peripheral swelling			

subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	7 / 7 (100.00%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	23	3	0
Swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Temperature intolerance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Erectile dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	3 / 7 (42.86%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	3	0	0
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			

subjects affected / exposed	0 / 7 (0.00%)	2 / 3 (66.67%)	1 / 2 (50.00%)
occurrences (all)	0	3	1
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lung consolidation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasal ulcer			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	2	0	1
Painful respiration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Productive cough			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rhinalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Rhinitis atrophic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sinus pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Wheezing			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Confusional state			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	2 / 2 (100.00%)
occurrences (all)	2	0	2
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	3 / 7 (42.86%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	5	2	0
Amylase abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 7 (42.86%)	3 / 3 (100.00%)	0 / 2 (0.00%)
occurrences (all)	5	3	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	4	0	2
Blood glucose increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Blood iron decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
C-reactive protein abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	7	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Procalcitonin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Troponin I increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Troponin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urobilinogen urine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Back injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Bone contusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Meniscus injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Mouth injury			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Rib fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sunburn			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Wound haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Wound secretion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Myocardial ischaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 7 (42.86%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	3	0	1
Dizziness postural			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
External compression headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Head discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	5 / 7 (71.43%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	7	4	0
Hyperaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypoaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Hyposmia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			

subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Peroneal nerve palsy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Leukopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0

Thrombocytopenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Thrombocytosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Middle ear effusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Tympanic membrane disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Chorioretinal disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Chorioretinopathy			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Eyelid rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Iridocyclitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Papilloedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Periorbital oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Periorbital swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vision blurred			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vitreous adhesions			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 7 (14.29%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	1	2	0
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Abdominal pain lower			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Angular cheilitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Change of bowel habit			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	2 / 2 (100.00%)
occurrences (all)	1	3	2
Diarrhoea			
subjects affected / exposed	5 / 7 (71.43%)	2 / 3 (66.67%)	2 / 2 (100.00%)
occurrences (all)	9	6	5
Dry mouth			
subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Frequent bowel movements			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	1	0

Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Large intestine perforation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lip blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lip disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Lip oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lip pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lip ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	3 / 7 (42.86%)	3 / 3 (100.00%)	1 / 2 (50.00%)
occurrences (all)	3	7	2
Oral disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Oral pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rectal tenesmus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Tongue disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tongue oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	1 / 3 (33.33%)	2 / 2 (100.00%)
occurrences (all)	2	1	2
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hepatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypertransaminasaemia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	2 / 7 (28.57%)	3 / 3 (100.00%)	0 / 2 (0.00%)
occurrences (all)	2	4	0
Drug eruption			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	1 / 2 (50.00%)
occurrences (all)	0	2	1
Erythema multiforme			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	3 / 7 (42.86%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	10	0	0

Macule			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	3 / 7 (42.86%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	7	0	0
Pain of skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Palmar erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	2 / 7 (28.57%)	3 / 3 (100.00%)	1 / 2 (50.00%)
occurrences (all)	6	5	1
Psoriasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Purpura			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	3 / 7 (42.86%)	2 / 3 (66.67%)	1 / 2 (50.00%)
occurrences (all)	8	5	3
Rash erythematous			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash follicular			

subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	1	0	1
Rash pruritic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Skin exfoliation			
subjects affected / exposed	0 / 7 (0.00%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Skin fissures			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Vitiligo			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Xeroderma			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hydronephrosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypopituitarism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypothyroidism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 7 (42.86%)	2 / 3 (66.67%)	1 / 2 (50.00%)
occurrences (all)	6	2	1
Arthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Back pain			

subjects affected / exposed	2 / 7 (28.57%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	3	0	1
Bone pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Bursitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Joint instability			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Limb mass			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	3	1	0
Muscular weakness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Neck mass			

subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	2 / 7 (28.57%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	2	1	0
Osteopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Winged scapula			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Fungal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Fungal skin infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Genital herpes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oral fungal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pneumonia klebsiella			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Rash pustular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 3 (33.33%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			

subjects affected / exposed	3 / 7 (42.86%)	2 / 3 (66.67%)	0 / 2 (0.00%)
occurrences (all)	4	2	0
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypophagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Polydipsia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part 2:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg	Part 2:pembrolizumab 2 mg/kg+trametinib 1.5 mg	Part 3:pembrolizumab 2 mg/kg+dabrafenib 150 mg+trametinib 2 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	2 / 2 (100.00%)	60 / 60 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	6
Cancer pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Deep vein thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Flushing			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	2	0	0
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	12
Hypertensive crisis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	6 / 60 (10.00%)
occurrences (all)	0	0	7
Lymphoedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Phlebitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	19 / 60 (31.67%)
occurrences (all)	0	0	33
Axillary pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Chest pain			

subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	3	0	2
Chills			
subjects affected / exposed	6 / 8 (75.00%)	0 / 2 (0.00%)	21 / 60 (35.00%)
occurrences (all)	12	0	59
Face oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	2
Facial pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	6 / 8 (75.00%)	1 / 2 (50.00%)	22 / 60 (36.67%)
occurrences (all)	10	2	37
Feeling abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	2	0	0
Feeling hot			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Generalised oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Impaired healing			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	8 / 60 (13.33%)
occurrences (all)	0	0	15
Localised oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Malaise			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Medical device site rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
Non-cardiac chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Oedema peripheral			
subjects affected / exposed	2 / 8 (25.00%)	2 / 2 (100.00%)	10 / 60 (16.67%)
occurrences (all)	2	2	13
Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	3
Peripheral swelling			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	8 / 8 (100.00%)	0 / 2 (0.00%)	50 / 60 (83.33%)
occurrences (all)	25	0	262
Swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Temperature intolerance			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Benign prostatic hyperplasia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Erectile dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	5 / 8 (62.50%)	1 / 2 (50.00%)	10 / 60 (16.67%)
occurrences (all)	6	1	17
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 2 (50.00%)	9 / 60 (15.00%)
occurrences (all)	2	1	11
Dyspnoea exertional			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	2	0	3
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lung consolidation			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	2	0	2
Nasal ulcer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences (all)	3	0	5
Painful respiration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	4 / 60 (6.67%)
occurrences (all)	0	1	6
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Respiratory distress			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rhinalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rhinitis atrophic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Sinus pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Depression			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	2	0	3
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			

subjects affected / exposed	2 / 8 (25.00%)	1 / 2 (50.00%)	11 / 60 (18.33%)
occurrences (all)	2	1	15
Amylase abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	5
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 8 (25.00%)	1 / 2 (50.00%)	12 / 60 (20.00%)
occurrences (all)	3	1	17
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	10 / 60 (16.67%)
occurrences (all)	2	0	18
Blood bilirubin increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	2
Blood cholesterol increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	5
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	5 / 60 (8.33%)
occurrences (all)	0	1	9
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	8
Blood glucose increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Blood iron decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase increased			

subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Blood potassium increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
C-reactive protein abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	7 / 60 (11.67%)
occurrences (all)	1	0	8
International normalised ratio increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	7
Liver function test abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			

subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	4	0	7
Neutrophil count increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	4	0	1
Procalcitonin increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	2	0	2
Troponin I increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Troponin increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Urobilinogen urine increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	6 / 60 (10.00%)
occurrences (all)	1	0	6
Weight increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
White blood cell count decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	2	0	2
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	4
Back injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Bone contusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Meniscus injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Mouth injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Rib fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Skin laceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Wound haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Wound secretion			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Myocardial ischaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	7 / 60 (11.67%)
occurrences (all)	1	0	8
Dizziness postural			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	2 / 60 (3.33%)
occurrences (all)	0	1	3
External compression headache			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Head discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	4 / 8 (50.00%)	0 / 2 (0.00%)	18 / 60 (30.00%)
occurrences (all)	6	0	29
Hyperaesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	3
Hyposmia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	4
Neuralgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	2
Peroneal nerve palsy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Syncope			

subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	2 / 60 (3.33%)
occurrences (all)	0	1	2
Taste disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	8 / 60 (13.33%)
occurrences (all)	1	0	13
Leukocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	3
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	2
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	3
Thrombocytosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Middle ear effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	4
Eye disorders			
Cataract			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Chorioretinal disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Chorioretinopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	4
Eyelid rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Iridocyclitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0

Keratitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Papilloedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Periorbital swelling			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Retinopathy			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Vision blurred			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	3	0	3
Visual field defect			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Vitreous adhesions			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Vitreous detachment			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Abdominal distension			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	2	0	7
Abdominal pain lower			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	9 / 60 (15.00%)
occurrences (all)	0	0	9
Angular cheilitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Change of bowel habit			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences (all)	1	0	7
Diarrhoea			

subjects affected / exposed	6 / 8 (75.00%)	0 / 2 (0.00%)	28 / 60 (46.67%)
occurrences (all)	8	0	90
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	8 / 60 (13.33%)
occurrences (all)	0	0	10
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	5
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Glossodynia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Large intestine perforation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lip blister			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lip disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lip oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Lip pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Lip ulceration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	2	0	3
Nausea			
subjects affected / exposed	5 / 8 (62.50%)	0 / 2 (0.00%)	23 / 60 (38.33%)
occurrences (all)	9	0	46
Oral disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Rectal tenesmus			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	5 / 60 (8.33%)
occurrences (all)	0	1	5
Tongue disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Tongue oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Vomiting			
subjects affected / exposed	5 / 8 (62.50%)	0 / 2 (0.00%)	22 / 60 (36.67%)
occurrences (all)	7	0	55
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Hepatitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Hypertransaminasaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Alopecia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences (all)	1	0	5
Dermatitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	6
Dermatitis acneiform			
subjects affected / exposed	4 / 8 (50.00%)	0 / 2 (0.00%)	9 / 60 (15.00%)
occurrences (all)	5	0	9
Drug eruption			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	7 / 60 (11.67%)
occurrences (all)	2	0	10
Eczema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	7 / 60 (11.67%)
occurrences (all)	1	0	12
Erythema multiforme			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	4
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	7
Macule			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	3
Nail disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	3
Pain of skin			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Palmar erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Pruritus			
subjects affected / exposed	2 / 8 (25.00%)	1 / 2 (50.00%)	10 / 60 (16.67%)
occurrences (all)	2	2	17
Psoriasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Purpura			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	4 / 8 (50.00%)	1 / 2 (50.00%)	27 / 60 (45.00%)
occurrences (all)	5	1	50
Rash erythematous			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Rash follicular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	2 / 60 (3.33%)
occurrences (all)	0	1	2
Rash maculo-papular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	6 / 60 (10.00%)
occurrences (all)	1	0	9
Rash pruritic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	4

Scab			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Skin fissures			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Skin haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Vitiligo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	12 / 60 (20.00%)
occurrences (all)	0	0	18
Xeroderma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hydronephrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	1	0	1
Renal failure			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Urinary tract pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	3	0	3
Hypopituitarism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences (all)	3	0	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 8 (50.00%)	0 / 2 (0.00%)	24 / 60 (40.00%)
occurrences (all)	12	0	54
Arthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 2 (50.00%)	8 / 60 (13.33%)
occurrences (all)	1	1	9
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Flank pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Joint instability			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Limb discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Limb mass			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	5	0	8
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	2
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Musculoskeletal stiffness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	16 / 60 (26.67%)
occurrences (all)	12	0	23
Neck mass			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	2	0	1
Osteopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	1 / 8 (12.50%)	1 / 2 (50.00%)	7 / 60 (11.67%)
occurrences (all)	2	1	11
Rotator cuff syndrome			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Winged scapula			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	3
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	5 / 60 (8.33%)
occurrences (all)	0	0	5
Cystitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	6
Ear infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Fungal skin infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Gastroenteritis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Genital herpes			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Gingivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	1	0	5
Oral candidiasis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Oral fungal infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	2	0	4
Paronychia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	4 / 60 (6.67%)
occurrences (all)	0	0	4
Pneumonia klebsiella			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Pustule			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 8 (37.50%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	3	0	4
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	6 / 60 (10.00%)
occurrences (all)	2	0	9
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	2 / 8 (25.00%)	0 / 2 (0.00%)	13 / 60 (21.67%)
occurrences (all)	2	0	17
Dehydration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	2
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	4
Hyperglycaemia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Hyperuricaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	0	0	5
Hypocalcaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	3
Hypokalaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 2 (50.00%)	6 / 60 (10.00%)
occurrences (all)	1	1	8
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 2 (50.00%)	1 / 60 (1.67%)
occurrences (all)	0	1	1
Hypophagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 2 (0.00%)	2 / 60 (3.33%)
occurrences (all)	1	0	2
Polydipsia			

subjects affected / exposed	0 / 8 (0.00%)	0 / 2 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 3:placebo+dabrafenib 150 mg+trametinib 2 mg	Part 4:4 weeks trametinib (Tra) 2mg; pembrolizumab+Tra 2mg	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 60 (96.67%)	3 / 3 (100.00%)	4 / 4 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Cancer pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Deep vein thrombosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flushing			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Hypertensive crisis			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	10 / 60 (16.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	13	1	0
Lymphoedema			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Phlebitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Thrombosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 60 (18.33%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	14	1	0
Axillary pain			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Catheter site pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	2 / 60 (3.33%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	2	1	0
Chills			
subjects affected / exposed	23 / 60 (38.33%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	51	0	2
Face oedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Facial pain			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	25 / 60 (41.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	41	1	0
Feeling abnormal			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Feeling hot			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Impaired healing			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	8 / 60 (13.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	12	0	0
Localised oedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Medical device site rash			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Mucosal inflammation			
subjects affected / exposed	1 / 60 (1.67%)	2 / 3 (66.67%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Non-cardiac chest pain			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	5 / 60 (8.33%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	5	2	1
Pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Peripheral swelling			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	41 / 60 (68.33%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	118	2	2
Swelling			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Temperature intolerance			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Erectile dysfunction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			

Atelectasis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	12 / 60 (20.00%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	12	2	2
Dysphonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	4 / 60 (6.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	4	0	1
Dyspnoea exertional			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Haemoptysis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lung consolidation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Nasal ulcer			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	8 / 60 (13.33%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	12	1	0

Painful respiration			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pulmonary embolism			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory distress			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinalgia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinitis atrophic			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Sinus pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Throat irritation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	11 / 60 (18.33%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	12	0	2
Amylase abnormal			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 60 (20.00%)	0 / 3 (0.00%)	3 / 4 (75.00%)
occurrences (all)	14	0	3
Blood alkaline phosphatase increased			

subjects affected / exposed	12 / 60 (20.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	16	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood cholesterol increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 60 (10.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	9	1	0
Blood creatinine increased			
subjects affected / exposed	5 / 60 (8.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	6	0	1
Blood glucose increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood iron decreased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Blood potassium increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
C-reactive protein abnormal			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ejection fraction decreased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 60 (16.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	14	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Liver function test abnormal			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Procalcitonin increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			

subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Troponin I increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Troponin increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urobilinogen urine increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	7 / 60 (11.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	8	0	0
Weight increased			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	8 / 60 (13.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	11	0	0
Back injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Bone contusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Meniscus injury			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Mouth injury			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sunburn			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Wound haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Wound secretion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Myocardial ischaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Palpitations			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 60 (13.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	10	0	0
Dizziness postural			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
External compression headache			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Head discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	13 / 60 (21.67%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	23	1	1
Hyperaesthesia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyposmia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Migraine			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neuralgia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Peroneal nerve palsy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	1
Taste disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0

Leukocytosis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	6 / 60 (10.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	9	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Middle ear effusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane disorder			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Chorioretinal disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Chorioretinopathy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Eyelid rash			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Iridocyclitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Papilloedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Periorbital swelling			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Retinopathy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Uveitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	7	0	1
Visual field defect			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Visual impairment			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vitreous adhesions			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			

subjects affected / exposed	4 / 60 (6.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Abdominal pain lower			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	3 / 60 (5.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Angular cheilitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Change of bowel habit			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	7 / 60 (11.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	7	1	0
Diarrhoea			
subjects affected / exposed	17 / 60 (28.33%)	3 / 3 (100.00%)	2 / 4 (50.00%)
occurrences (all)	29	4	3
Dry mouth			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Dyspepsia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Dysphagia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 60 (6.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	5	0	0
Glossodynia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematemesis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Intestinal obstruction			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Large intestine perforation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lip blister			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lip disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lip oedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lip pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lip ulceration			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 60 (0.00%)	2 / 3 (66.67%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Nausea			
subjects affected / exposed	28 / 60 (46.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	47	0	1
Oral disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Proctalgia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rectal tenesmus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Tongue disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tongue oedema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Toothache			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	17 / 60 (28.33%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	29	0	1
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hepatitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hypertransaminasaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Alopecia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Dermatitis acneiform			
subjects affected / exposed	4 / 60 (6.67%)	3 / 3 (100.00%)	3 / 4 (75.00%)
occurrences (all)	4	4	7
Drug eruption			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	4 / 60 (6.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	4	1	0
Eczema			

subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	4 / 60 (6.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Erythema multiforme			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Erythema nodosum			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hyperhidrosis			
subjects affected / exposed	6 / 60 (10.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	10	0	0
Macule			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Pain of skin			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Palmar erythema			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Pruritus			
subjects affected / exposed	9 / 60 (15.00%)	1 / 3 (33.33%)	1 / 4 (25.00%)
occurrences (all)	12	1	1

Psoriasis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Purpura			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	18 / 60 (30.00%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	24	0	2
Rash erythematous			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash follicular			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Rash maculo-papular			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	5	0	1
Rash pruritic			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Scab			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin fissures			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Skin haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Vitiligo			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Xeroderma			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Haematuria			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hydronephrosis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Urinary tract pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypopituitarism			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 60 (28.33%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	34	0	2
Arthritis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Back pain			
subjects affected / exposed	3 / 60 (5.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	3	1	0
Bone pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Bursitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Joint instability			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Limb mass			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	10 / 60 (16.67%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	17	0	3
Neck mass			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Osteopenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	7	0	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Winged scapula			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Cellulitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	4 / 60 (6.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	7	0	0
Ear infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	1 / 60 (1.67%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Genital herpes			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Herpes zoster			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0

Nasopharyngitis			
subjects affected / exposed	6 / 60 (10.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	6	0	0
Oral candidiasis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Oral fungal infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Paronychia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	2	0	1
Pneumonia klebsiella			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pustule			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Tonsillitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 60 (3.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Urinary tract infection			
subjects affected / exposed	5 / 60 (8.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	7	0	0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	11 / 60 (18.33%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	11	0	0
Dehydration			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Hyperphosphataemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			

subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	4 / 60 (6.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	3 / 60 (5.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	4 / 60 (6.67%)	0 / 3 (0.00%)	2 / 4 (50.00%)
occurrences (all)	5	0	4
Hypophagia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 3 (33.33%)	2 / 4 (50.00%)
occurrences (all)	0	1	3
Polydipsia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 3 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 4:4 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg	Part 4:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent	Part 4:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg intermittent
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	6 / 6 (100.00%)	3 / 3 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cancer pain			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Melanocytic naevus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Deep vein thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Flushing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Hypertensive crisis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Lymphoedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Catheter site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	3 / 5 (60.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	5	1	0
Face oedema			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Facial pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	4 / 6 (66.67%)	1 / 3 (33.33%)
occurrences (all)	1	4	1
Feeling abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Feeling cold			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Feeling hot			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Generalised oedema			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Impaired healing			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Medical device site rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	1 / 3 (33.33%)
occurrences (all)	2	3	2
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	3 / 6 (50.00%)	1 / 3 (33.33%)
occurrences (all)	1	4	1
Swelling			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Temperature intolerance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erectile dysfunction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	1 / 5 (20.00%)	3 / 6 (50.00%)	1 / 3 (33.33%)
occurrences (all)	1	3	1
Dysphonia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Epistaxis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haemoptysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Laryngeal inflammation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lung consolidation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Nasal ulcer			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Painful respiration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Pneumonitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	2 / 3 (66.67%)
occurrences (all)	1	0	2
Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rales			

subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Respiratory distress			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rhinalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinitis atrophic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Depression			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Insomnia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	2	3	0
Amylase abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	4	4	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	2	3	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood iron decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood uric acid increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Body temperature increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
C-reactive protein abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lipase increased			

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Liver function test abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Procalcitonin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Troponin I increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Troponin increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urobilinogen urine increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Back injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bone contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Meniscus injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Mouth injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Procedural pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin laceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sunburn			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Wound haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Wound secretion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Left ventricular dysfunction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Myocardial ischaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Palpitations			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	2	2	2
Dizziness postural			

subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	2
External compression headache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Head discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	4	0
Hyperaesthesia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Hyposmia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Peroneal nerve palsy			

subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Taste disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	3 / 6 (50.00%)	1 / 3 (33.33%)
occurrences (all)	0	3	1
Leukocytosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lymphadenopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Thrombocytosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Deafness unilateral			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ear discomfort			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Middle ear effusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tympanic membrane disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Chorioretinal disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Chorioretinopathy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Eyelid rash			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Iridocyclitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Keratitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Papilloedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Periorbital swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Retinopathy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Uveitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	2 / 3 (66.67%)
occurrences (all)	0	1	2
Visual field defect			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Visual impairment			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Vitreous adhesions			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	4	0
Abdominal pain lower			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Angular cheilitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ascites			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Change of bowel habit			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Constipation			
subjects affected / exposed	1 / 5 (20.00%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	2	3	0
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)	5 / 6 (83.33%)	1 / 3 (33.33%)
occurrences (all)	5	15	1
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Haematemesis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Intestinal obstruction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Large intestine perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lip blister			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Lip disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lip oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Lip pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Lip ulceration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	3 / 5 (60.00%)	3 / 6 (50.00%)	2 / 3 (66.67%)
occurrences (all)	3	5	2
Oral disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Proctalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Rectal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Rectal tenesmus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tongue disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tongue oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	1 / 3 (33.33%)
occurrences (all)	3	8	1
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hepatitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Alopecia			

subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Dermatitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	2 / 5 (40.00%)	5 / 6 (83.33%)	1 / 3 (33.33%)
occurrences (all)	5	6	1
Drug eruption			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	2	2	1
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Erythema multiforme			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Erythema nodosum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Macule			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nail disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Night sweats			

subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Pain of skin			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Palmar erythema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	2 / 5 (40.00%)	2 / 6 (33.33%)	2 / 3 (66.67%)
occurrences (all)	3	2	3
Psoriasis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Purpura			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	2 / 5 (40.00%)	2 / 6 (33.33%)	3 / 3 (100.00%)
occurrences (all)	3	2	5
Rash erythematous			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash follicular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Rash pruritic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Scab			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Skin exfoliation			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Skin fissures			
subjects affected / exposed	1 / 5 (20.00%)	3 / 6 (50.00%)	0 / 3 (0.00%)
occurrences (all)	2	4	0
Skin haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Vitiligo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Xeroderma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hydronephrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			

subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Renal failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urinary tract pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypopituitarism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypothyroidism			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Arthritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Bone pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Bursitis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Joint instability			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Limb mass			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Muscular weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 5 (20.00%)	2 / 6 (33.33%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Neck mass			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Osteopenia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rotator cuff syndrome			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Winged scapula			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Conjunctivitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Fungal skin infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Genital herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Gingivitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Herpes virus infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Oral candidiasis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Oral fungal infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	2 / 5 (40.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0

Pneumonia klebsiella			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pustule			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	1	1	1
Dehydration			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	3	1	0
Hypercalcaemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 3 (0.00%)
occurrences (all)	1	2	0
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Hypophagia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Polydipsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part 5:2 weeks Tra 1.5mg; pembrolizumab+Tra 1.5mg	Part 5:2 weeks Tra 2mg; pembrolizumab+Tra 2mg intermittent	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	9 / 9 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Cancer pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Melanocytic naevus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Deep vein thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hot flush			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	

Hypertensive crisis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	4	1	
Axillary pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Catheter site pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Face oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Facial pain			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	3 / 12 (25.00%)	3 / 9 (33.33%)	
occurrences (all)	3	3	
Feeling abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Feeling cold			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Feeling hot			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Generalised oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Impaired healing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Localised oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Medical device site rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Mucosal inflammation			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Non-cardiac chest pain			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	4 / 12 (33.33%)	4 / 9 (44.44%)	
occurrences (all)	5	4	
Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	0 / 12 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	7 / 12 (58.33%)	3 / 9 (33.33%)	
occurrences (all)	14	4	
Swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Temperature intolerance			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Erectile dysfunction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			

Atelectasis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	4 / 12 (33.33%)	1 / 9 (11.11%)	
occurrences (all)	6	1	
Dysphonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	2 / 12 (16.67%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Haemoptysis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Laryngeal inflammation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Lung consolidation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nasal ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Painful respiration			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rales			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Respiratory distress			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rhinalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rhinitis allergic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rhinitis atrophic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sinus pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Throat irritation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Wheezing			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Confusional state			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Depression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	6 / 12 (50.00%)	3 / 9 (33.33%)	
occurrences (all)	8	5	
Amylase abnormal			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Amylase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 12 (50.00%)	5 / 9 (55.56%)	
occurrences (all)	10	8	
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 12 (16.67%)	3 / 9 (33.33%)	
occurrences (all)	2	3	
Blood bilirubin increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Blood glucose increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Blood iron decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Blood potassium increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Blood uric acid increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Body temperature increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
C-reactive protein abnormal			

subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Ejection fraction decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
International normalised ratio increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lipase increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 9 (22.22%)	
occurrences (all)	1	3	
Liver function test abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neutrophil count increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Procalcitonin increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			

subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Troponin I increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Troponin increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Urobilinogen urine increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Back injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Bone contusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Meniscus injury			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Mouth injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rib fracture			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Skin laceration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sunburn			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Wound haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Wound secretion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Myocardial ischaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Palpitations			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sinus bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Tachycardia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dizziness postural			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
External compression headache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Head discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	4 / 12 (33.33%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Hyperaesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hyposmia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Migraine			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neuralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Peroneal nerve palsy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Seizure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Taste disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 12 (50.00%)	1 / 9 (11.11%)	
occurrences (all)	6	1	

Leukocytosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Leukopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Thrombocytosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Deafness unilateral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Middle ear effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Tympanic membrane disorder			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Chorioretinal disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Chorioretinopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dry eye			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eyelid rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Iridocyclitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Keratitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ocular hyperaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Papilloedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Periorbital oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Periorbital swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Retinopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Uveitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Visual field defect			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vitreous adhesions			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vitreous detachment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			

subjects affected / exposed	1 / 12 (8.33%)	3 / 9 (33.33%)	
occurrences (all)	1	4	
Abdominal pain lower			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Angular cheilitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	0 / 12 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Change of bowel habit			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	2 / 12 (16.67%)	3 / 9 (33.33%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	5 / 12 (41.67%)	5 / 9 (55.56%)	
occurrences (all)	12	11	
Dry mouth			
subjects affected / exposed	2 / 12 (16.67%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Dysphagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Frequent bowel movements			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Glossodynia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Haematemesis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Intestinal obstruction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Large intestine perforation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lip blister			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lip disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lip oedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lip pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lip ulceration			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Mouth ulceration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 12 (25.00%)	2 / 9 (22.22%)	
occurrences (all)	4	2	
Oral disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oral pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Proctalgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rectal tenesmus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tongue disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Tongue oedema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Toothache			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	2 / 12 (16.67%)	2 / 9 (22.22%)	
occurrences (all)	2	3	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hepatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Dermatitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dermatitis acneiform			
subjects affected / exposed	3 / 12 (25.00%)	6 / 9 (66.67%)	
occurrences (all)	4	7	
Drug eruption			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dry skin			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Eczema			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Erythema multiforme			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Erythema nodosum			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hyperhidrosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Macule			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nail disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Night sweats			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pain of skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Palmar erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	6 / 12 (50.00%)	3 / 9 (33.33%)	
occurrences (all)	10	3	

Psoriasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Purpura			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	6 / 12 (50.00%)	3 / 9 (33.33%)	
occurrences (all)	11	6	
Rash erythematous			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash follicular			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Scab			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Skin exfoliation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Skin fissures			
subjects affected / exposed	2 / 12 (16.67%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Skin haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

Vitiligo			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Xeroderma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Bladder spasm			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Dysuria			
subjects affected / exposed	2 / 12 (16.67%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hydronephrosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pollakiuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Renal failure			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Urinary tract pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypopituitarism			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Arthritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Bursitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Flank pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Joint instability			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Limb discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Limb mass			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			

subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Muscular weakness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Neck mass			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Osteopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Winged scapula			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Catheter site infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Fungal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Fungal skin infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Genital herpes			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gingivitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Herpes virus infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oral fungal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Paronychia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Pustule			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Rash pustular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Decreased appetite			
subjects affected / exposed	2 / 12 (16.67%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Hyperphosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hyperuricaemia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypocalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypomagnesaemia			
subjects affected / exposed	3 / 12 (25.00%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypophagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Hypophosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Polydipsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2015	Amendment 01 removed the MK-3475 10 mg/kg administered on Day 1 of each 2-week cycle (Q2W) dose/schedule and all associated combination treatment arms using the 10 mg/kg Q2W dose/schedule and implemented the monotherapy dose/schedule for MK-3475 at 2 mg/kg administered on Day 1 of each 3-week cycle (Q3W).
19 October 2016	Amendment 02 incorporated study Parts 4 and 5 that included additional dosing regimens to identify, confirm, and expand a tolerable dose level of pembrolizumab and trametinib in BRAF wild-type melanoma and solid tumor participants.
22 January 2018	Amendment 03 implemented a safety update regarding myocarditis, updated the protocol for compliance with the latest dose modification guidance, and clarified the collection of survivor information throughout and following study participation regardless of discontinuation of treatment.
26 July 2018	Amendment 04 unblinded participants in Part 3 as a result of final analysis. The option for entering the second course phase of treatment was discontinued and language was added to transition participants to an extension study to continue protocol-defined assessments and treatment. The collection of data for pharmacokinetics, anti-drug antibodies, and patient reported outcomes questionnaires was discontinued since sufficient data were collected to complete the planned analysis.
13 May 2019	Amendment 05 removed enrollment for the Part 5 dose expansion phase from the protocol and updated language for contraception requirements and rash management.
19 January 2020	Amendment 06 added dose modification requirements for cases of severe cutaneous adverse reactions (SCARs) that have been reported during treatment with dabrafenib in combination with trametinib.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported