Clinical trial results:
A Phase 1/2 Study of Nivolumab (IND# 124729) in Children, Adolescents, and Young Adults with Recurrent or Refractory Solid Tumors as a Single Agent and in Combination with Ipilimumab

Summary

EudraCT number	2014-005674-11
Trial protocol	Outside EU/EEA
Global end of trial date	02 November 2022

Results information

Result version number	v1 (current)
This version publication date	18 November 2023
First version publication date	18 November 2023

Trial information

Trial identification

Sponsor protocol code	CA209-070

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02304458
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Cancer Institute (NCI)
Sponsor organisation address	9609 Medical Center Drive, Bethesda, United States,
Public contact	National Cancer Institute, National Institutes of Health, National Cancer Institute (NCI), 001 1-800-422-6237, NCIinfo@nih.gov
Scientific contact	National Cancer Institute, National Institutes of Health, National Cancer Institute (NCI), 001 1-800-422-6237, NCIinfo@nih.gov

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001407-PIP01-12
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Determine the tolerability, define and describe the toxicities of nivolumab administered as a single agent at 3 mg/kg.
- Determine if systemic nivolumab exposure in children is similar to the systemic exposure in adults following a 3 mg/kg dose.
- Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) and define and describe the toxicities of nivolumab plus ipilimumab
- Assess antitumor effects of nivolumab across selected childhood solid tumors
- Assess antitumor effects of nivolumab in combination with ipilimumab across selected childhood solid tumors in two dose combinations
- Characterize the pharmacokinetics of nivolumab alone and in combination with ipilimumab, including AUC, Cmax, Cmin, using intensive sampling.
- Assess immunogenicity of nivolumab alone and in combination with ipilimumab by measuring anti-drug antibody (ADA) levels

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 133
Worldwide total number of subjects	134
EEA total number of subjects	0

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)	1
Children (2-11 years)	44
Adolescents (12-17 years)	55
Adults (18-64 years)	34
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Note: The Neuroblastoma cohorts D1 and D6, and Non-Hodgkin's Lymphoma cohort D5 were not opened to accrual as they did not meet the threshold for the statistical design. So no data were available for the Non-Hodgkin Lymphoma and Neuroblastoma cohorts.

AE- Adverse event
PD- Progressive disease

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Nivo 3 mg/kg

Arm description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days.

A1: Recurrent or refractory solid tumors, without
CNS tumors or known CNS metastases.

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

Dosage and administration details:

3 mg/kg Q2 week

Arm title	Part B: Nivo 3 mg/kg

Arm description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days.

B1: Relapsed or refractory neuroblastoma
B2: Relapsed or refractory osteosarcoma
B3: Relapsed or refractory rhabdomyosarcoma
B4: Relapsed or refractory Ewing sarcoma or Peripheral PNET
B5: Relapsed or refractory Hodgkin Lymphoma
B6: Relapsed or refractory non-Hodgkin Lymphoma
B7: Unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma
B8: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

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

Dosage and administration details:

3 mg/kg Q2 week

Arm title	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg

Arm description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C1: Recurrent or refractory solid tumors, without CNS tumors or known CNS metastases.

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

Dosage and administration details:

1 mg/kg Q2 week

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

Dosage and administration details:

1 mg/kg Q2 week

Arm title	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg

Arm description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C2: Recurrent or refractory solid tumors, without CNS tumors or known CNS metastases.

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

Dosage and administration details:

1 mg/kg Q2 week

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

Dosage and administration details:

3 mg/kg Q2 week

Arm title	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg

Arm description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part D, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

D1: Relapsed or refractory neuroblastoma
D2: Relapsed or refractory osteosarcoma
D3: Relapsed or refractory rhabdomyosarcoma
D4: Relapsed or refractory Ewing Sarcoma or Peripheral PNET
D5: Relapsed or refractory non-Hodgkin Lymphoma
D6: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

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

Dosage and administration details:

1 mg/kg Q2 week

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

Dosage and administration details:

3 mg/kg Q2 week

Arm title	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg

Arm description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part E; in cycle 5 and for subsequent cycles, cycle length was 28 days and nivolumab 3 mg/kg was to be administered on days 1 and 15 of each cycle.

E3: Relapsed or refractory rhabdomyosarcoma
E4: Relapsed or refractory Ewing Sarcoma or Peripheral PNET

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

Dosage and administration details:

1 mg/kg Q2 week

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

Dosage and administration details:

1 mg/kg Q2 week

Number of subjects in period 1	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg
Started	12	68	6
Completed	0	0	0
Not completed	12	68	6
PD > 12 weeks after start of protocol therapy	3	8	2
5th anniversary of study entry	-	1	-
Physician decision	1	14	1
Death	1	3	-
PD > 40% increase from baseline target lesions	6	29	3
AE requiring removal from protocol therapy	-	7	-
Refusal of further protocol therapy	1	6	-

Number of subjects in period 1	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg
Started	12	28	8
Completed	0	0	0
Not completed	12	28	8
PD > 12 weeks after start of protocol therapy	2	4	-
5th anniversary of study entry	-	-	-
Physician decision	-	2	-
Death	-	1	-
PD > 40% increase from baseline target lesions	10	17	4
AE requiring removal from protocol therapy	-	3	4
Refusal of further protocol therapy	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Part A: Nivo 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days.

A1: Recurrent or refractory solid tumors, without
CNS tumors or known CNS metastases.

Reporting group title	Part B: Nivo 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days.

B1: Relapsed or refractory neuroblastoma
B2: Relapsed or refractory osteosarcoma
B3: Relapsed or refractory rhabdomyosarcoma
B4: Relapsed or refractory Ewing sarcoma or Peripheral PNET
B5: Relapsed or refractory Hodgkin Lymphoma
B6: Relapsed or refractory non-Hodgkin Lymphoma
B7: Unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma
B8: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

Reporting group title	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C1: Recurrent or refractory solid tumors, without
CNS tumors or known CNS metastases.

Reporting group title	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C2: Recurrent or refractory solid tumors, without
CNS tumors or known CNS metastases.

Reporting group title	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part D, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

D1: Relapsed or refractory neuroblastoma
D2: Relapsed or refractory osteosarcoma
D3: Relapsed or refractory rhabdomyosarcoma
D4: Relapsed or refractory Ewing Sarcoma or Peripheral PNET
D5: Relapsed or refractory non-Hodgkin Lymphoma
D6: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

Reporting group title	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part E; in cycle 5 and for subsequent cycles, cycle length was 28 days and nivolumab 3 mg/kg was to be administered on days 1 and 15 of each cycle.

E3: Relapsed or refractory rhabdomyosarcoma

Reporting group values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg
Number of subjects	12	68	6
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0	1	0
Children (2-11 years)	6	24	0
Adolescents (12-17 years)	6	27	6
Adults (18-64 years)	0	16	0
Gender Categorical Units: Subjects			
Female	5	26	1
Male	7	42	5
Race Categorical Units: Subjects			
White	12	48	3
Black or African American	0	9	1
American Indian or Alaska Native	0	0	0
Asian	0	6	1
Unkown/Not Reported	0	5	1
Ethnicity Categorical Units: Subjects			
Hispanic or Latino	2	9	1
Not Hispanic or Latino	10	58	5
Unkown/Not Reported	0	1	0

Reporting group values	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg
Number of subjects	12	28	8
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	6	7	1
Adolescents (12-17 years)	6	8	2
Adults (18-64 years)	0	13	5
Gender Categorical Units: Subjects			
Female	7	8	5
Male	5	20	3
Race Categorical Units: Subjects			
White	8	22	8
Black or African American	1	2	0
American Indian or Alaska Native	1	0	0
Asian	1	0	0

Unkown/Not Reported	1	4	0
Ethnicity Categorical Units: Subjects			
Hispanic or Latino	2	5	1
Not Hispanic or Latino	10	21	5
Unkown/Not Reported	0	2	2

Reporting group values	Total		
Number of subjects	134		
Age Categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	1		
Children (2-11 years)	44		
Adolescents (12-17 years)	55		
Adults (18-64 years)	34		
Gender Categorical Units: Subjects			
Female	52		
Male	82		
Race Categorical Units: Subjects			
White	101		
Black or African American	13		
American Indian or Alaska Native	1		
Asian	8		
Unkown/Not Reported	11		
Ethnicity Categorical Units: Subjects			
Hispanic or Latino	20		
Not Hispanic or Latino	109		
Unkown/Not Reported	5		

End points

End points reporting groups

Reporting group title	Part A: Nivo 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days.

A1: Recurrent or refractory solid tumors, without
CNS tumors or known CNS metastases.

Reporting group title	Part B: Nivo 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days.

B1: Relapsed or refractory neuroblastoma
B2: Relapsed or refractory osteosarcoma
B3: Relapsed or refractory rhabdomyosarcoma
B4: Relapsed or refractory Ewing sarcoma or Peripheral PNET
B5: Relapsed or refractory Hodgkin Lymphoma
B6: Relapsed or refractory non-Hodgkin Lymphoma
B7: Unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma
B8: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

Reporting group title	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C1: Recurrent or refractory solid tumors, without
CNS tumors or known CNS metastases.

Reporting group title	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C2: Recurrent or refractory solid tumors, without
CNS tumors or known CNS metastases.

Reporting group title	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part D, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

D1: Relapsed or refractory neuroblastoma
D2: Relapsed or refractory osteosarcoma
D3: Relapsed or refractory rhabdomyosarcoma
D4: Relapsed or refractory Ewing Sarcoma or Peripheral PNET
D5: Relapsed or refractory non-Hodgkin Lymphoma
D6: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

Reporting group title	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part E; in cycle 5 and for subsequent cycles, cycle length was 28 days and nivolumab 3 mg/kg was to be administered on days 1 and 15 of each cycle.

E3: Relapsed or refractory rhabdomyosarcoma

Subject analysis set title	Part B1: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with neuroblastoma receive nivolumab 3 mg/kg Q2 week IV	
Subject analysis set title	Part B2: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with osteosarcoma receive nivolumab 3 mg/kg Q2 week IV	
Subject analysis set title	Part B3: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with rhabdomyosarcoma receive nivolumab 3 mg/kg Q2 week IV	
Subject analysis set title	Part B4: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with Ewing sarcoma receive nivolumab 3 mg/kg Q2 week IV	
Subject analysis set title	Part B5: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with Hodgkin lymphoma receive nivolumab 3 mg/kg Q2 week IV	
Subject analysis set title	Part B6: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with non-Hodgkin lymphoma receive nivolumab 3 mg/kg Q2 week IV	
Subject analysis set title	Part B7: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with melanoma receive nivolumab 3 mg/kg Q2 week IV	
Subject analysis set title	Part B8: Nivo 3 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants with evaluable disease without measurable disease in patients with neuroblastoma receive nivolumab 3 mg/kg Q2 week IV	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1][2]
End point description: The percentage of participants with a best overall response of partial or complete response assessed per Response Evaluation Criteria in Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI. Complete Response (CR) = Disappearance of all target lesions. Partial Response (PR) = >=30% decrease in the sum of the longest diameter of target lesions.	
End point type	Primary
End point timeframe: From first dose until disease progression/recurrence (up to approximately 7 years)	

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: Only summary statistics 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: Endpoint is specific to only certain study arms

End point values	Part A: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	12	28
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.0 to 26.5)	0.0 (0.0 to 45.9)	0.0 (0.0 to 26.5)	7.1 (0.9 to 23.5)

End point values	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg	Part B1: Nivo 3 mg/kg	Part B2: Nivo 3 mg/kg	Part B3: Nivo 3 mg/kg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	10	10	10
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.0 to 36.9)	0.0 (0.0 to 30.8)	0.0 (0.0 to 30.8)	0.0 (0.0 to 30.8)

End point values	Part B4: Nivo 3 mg/kg	Part B5: Nivo 3 mg/kg	Part B6: Nivo 3 mg/kg	Part B7: Nivo 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	10	10	1
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.0 to 30.8)	30.0 (6.7 to 65.2)	10.0 (0.3 to 44.5)	0.0 (0.0 to 97.5)

End point values	Part B8: Nivo 3 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Percentage of Participants				
number (confidence interval 95%)	0.0 (0.0 to 41.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Response (TTR)

End point title	Time to Response (TTR)[3][4]

End point description:

The time from the date of first dose of study medication to the first response date (CR or PR whichever occurred first), as assessed by the investigator and confirmed by Central Review. TTR will be evaluated for responders only. Complete Response (CR) = Disappearance of all target lesions. Partial Response (PR) = >=30% decrease in the sum of the longest diameter of target lesions. Note: 99999 = N/A

End point type	Primary

End point timeframe:

From first dose to the date the response was first observed (up to approximately 7 years)

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: Only summary statistics 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: Endpoint is specific to only certain study arms

End point values	Part A: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[5]	0[6]	0[7]	2
Units: Months				
arithmetic mean (standard deviation)	()	()	()	2.09 (± 0.02)

Notes:

[5] - No participants had a response (CR/PR).

[6] - No participants had a response (CR/PR).

[7] - No participants had a response (CR/PR).

End point values	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg	Part B1: Nivo 3 mg/kg	Part B2: Nivo 3 mg/kg	Part B3: Nivo 3 mg/kg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[8]	0[9]	0[10]	0[11]
Units: Months				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[8] - No participants had a response (CR/PR).

[9] - No participants had a response (CR/PR).

[10] - No participants had a response (CR/PR).

[11] - No participants had a response (CR/PR).

End point values	Part B4: Nivo 3 mg/kg	Part B5: Nivo 3 mg/kg	Part B6: Nivo 3 mg/kg	Part B7: Nivo 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[12]	3	1	0[13]
Units: Months				
arithmetic mean (standard deviation)	()	2.25 (± 0.40)	8.64 (± 99999)	()

Notes:

[12] - No participants had a response (CR/PR).

[13] - No participants had a response (CR/PR).

End point values	Part B8: Nivo 3 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	0[14]			
Units: Months				
arithmetic mean (standard deviation)	()			

Notes:

[14] - No participants had a response (CR/PR).

Statistical analyses

No statistical analyses for this end point

Primary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[15][16]

End point description:

The time between the first response date (CR or PR whichever is recorded first), as determined by the investigator and confirmed by Central Review, to the date of the first documented tumor progression or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. For subjects who neither progress nor die, DOR will be censored on the date of their last evaluable tumor assessment. DOR will be evaluated for responders only. Complete Response (CR) = Disappearance of all target lesions. Partial Response (PR) = >=30% decrease in the sum of the longest diameter of target lesions. Note: 99999 = N/A

End point type	Primary

End point timeframe:

From first dose to the date of the first documented tumor progression or death due to any cause, whichever occurs first (up to approximately 7 years)

Notes:

[15] - 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: Only summary statistics planned for this endpoint

[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: Endpoint is specific to only certain study arms

End point values	Part A: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[17]	0[18]	0[19]	2
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	99999 (99999 to 99999)

Notes:

[17] - No participants had a response (CR/PR).

[18] - No participants had a response (CR/PR).

[19] - No participants had a response (CR/PR).

End point values	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg	Part B1: Nivo 3 mg/kg	Part B2: Nivo 3 mg/kg	Part B3: Nivo 3 mg/kg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[20]	0[21]	0[22]	0[23]
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[20] - No participants had a response (CR/PR).

[21] - No participants had a response (CR/PR).

[22] - No participants had a response (CR/PR).

[23] - No participants had a response (CR/PR).

End point values	Part B4: Nivo 3 mg/kg	Part B5: Nivo 3 mg/kg	Part B6: Nivo 3 mg/kg	Part B7: Nivo 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[24]	3	1	0[25]
Units: Months				
median (confidence interval 95%)	(to)	1.87 (0.95 to 99999)	99999 (99999 to 99999)	(to)

Notes:

[24] - No participants had a response (CR/PR).

[25] - No participants had a response (CR/PR).

End point values	Part B8: Nivo 3 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	0[26]			
Units: Months				
median (confidence interval 95%)	(to)			

Notes:

[26] - No participants had a response (CR/PR).

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[27][28]

End point description:

The time from the date of first dose of study medication to the date of death from any cause. For subjects that are alive, their survival time will be censored at the date of last contact date (or "last known alive date"). Note: -99999 and 99999 = N/A

End point type	Primary

End point timeframe:

From the date of first dose to the date of death from any cause (up to approximately 7 years)

Notes:

[27] - 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: Only summary statistics planned for this endpoint

[28] - 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: Endpoint is specific to only certain study arms

End point values	Part A: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	6	12	28
Units: Months				
median (confidence interval 95%)	27.63 (1.87 to 99999)	18.50 (8.25 to 99999)	8.25 (5.45 to 99999)	6.44 (3.32 to 19.91)

End point values	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg	Part B1: Nivo 3 mg/kg	Part B2: Nivo 3 mg/kg	Part B3: Nivo 3 mg/kg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	10	10	10
Units: Months				
median (confidence interval 95%)	99999 (1.12 to 99999)	7.00 (2.33 to 14.06)	6.67 (2.23 to 7.39)	3.58 (0.76 to 6.37)

End point values	Part B4: Nivo 3 mg/kg	Part B5: Nivo 3 mg/kg	Part B6: Nivo 3 mg/kg	Part B7: Nivo 3 mg/kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	10	10	1
Units: Months				
median (confidence interval 95%)	6.47 (0.10 to 99999)	99999 (99999 to 99999)	22.47 (0.89 to 99999)	4.99 (-99999 to 99999)

End point values	Part B8: Nivo 3 mg/kg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Months				
median (confidence interval 95%)	99999 (2.99 to 99999)			

Statistical analyses

No statistical analyses for this end point

Primary: The Number of Participants Experiencing Adverse Events (AE)

End point title	The Number of Participants Experiencing Adverse Events

End point description:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in participants administered a study drug and that does not necessarily have a causal relationship with the treatment.

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category (e.g., pulmonary events, gastrointestinal events categories, etc.).

Other events of special interest (OEOSI) consist of a list of preferred terms grouped by specific category (e.g., Myositis Event, Myocarditis Event, Demyelination Event, Guillain-Barre Syndrome, Pancreatitis Event, Uveitis Event, Encephalitis Event, Myasthenic Syndrome, Rhabdomyolysis Event, Graft Versus Host Disease). Note: Events only included in the below table if a participants experienced an event of interest.

End point type	Primary

End point timeframe:

From first dose to 100 days after last dose of study therapy (up to approximately 63 months)

Notes:

[29] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	68	6	12
Units: Participants				
Adverse Events (AE)	12	68	6	12
Serious Adverse Events (SAE)	7	39	3	5
Drug-Related AE	12	60	6	12
Drug-Related SAE	3	14	1	2
AE Leading to Discontinuation	1	14	0	1
Drug-Related Gastrointestinal AE	2	4	0	0
Drug-Related Heptaic AE	6	26	1	4
Drug-Related Pulmonary AE	0	0	0	0
Drug-Related Renal AE	1	6	1	1
Drug-Related Skin AE	6	10	3	4
Drug-Related Hypersensitivity/Infusion Reaction AE	1	3	0	1
Pancreatitis Event	1	1	0	0
Uveitis Event	0	0	1	0
Graft Versus Host Disease Event	0	1	0	0

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	8		
Units: Participants				
Adverse Events (AE)	28	8		
Serious Adverse Events (SAE)	15	6		
Drug-Related AE	28	7		
Drug-Related SAE	6	5		
AE Leading to Discontinuation	5	0		
Drug-Related Gastrointestinal AE	4	3		
Drug-Related Heptaic AE	8	6		
Drug-Related Pulmonary AE	1	1		
Drug-Related Renal AE	5	1		

Drug-Related Skin AE	5	2		
Drug-Related Hypersensitivity/Infusion Reaction AE	1	1		
Pancreatitis Event	2	0		
Uveitis Event	0	0		
Graft Versus Host Disease Event	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: The Number of Participants with Dose Limiting Toxicities (DLT) During the First Cycle of Therapy

End point title	The Number of Participants with Dose Limiting Toxicities (DLT) During the First Cycle of Therapy[30][31]

End point description:

A DLT will be defined as any specific events that are possibly, probably, or definitely attributable to protocol therapy.

End point type	Primary

End point timeframe:

From first dose of study drug through the first 28 days for Part A and 21 days for Part C of treatment.

Notes:

[30] - 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: Only summary statistics planned for this endpoint

[31] - 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: Endpoint is specific to only certain study arms

End point values	Part A: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	6	12	
Units: Participants	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of PD-L1 Tumor Cell Expression Status

End point title	Frequency of PD-L1 Tumor Cell Expression Status[32]

End point description:

PD-L1 expression is defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry (IHC) assay. This is referred to as quantifiable PD-L1 expression. Analyzed in participants WITH PD-L1 QUANTIFIABLE AT BASELINE only.

End point type	Primary

End point timeframe:

Pre-study, and if a participant requires a biopsy for surgery and tumor tissue is removed, tissue will be analyzed for PD-L1 Expression (up to approximately 7 years)

Notes:

[32] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	54	5	10
Units: Percent of tumor cells				
arithmetic mean (standard deviation)	10.0 (± 22.2)	22.2 (± 39.9)	2.2 (± 4.9)	10.7 (± 31.4)

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	7		
Units: Percent of tumor cells				
arithmetic mean (standard deviation)	1.3 (± 5.1)	0.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Primary: The Numbers of Participants who Died During the Study

End point title	The Numbers of Participants who Died During the Study[33]

End point description:

The numbers of participants who died during the study.

End point type	Primary

End point timeframe:

From first dose to 100 days after last dose of study therapy (up to approximately 63 months)

Notes:

[33] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	68	6	12
Units: Participants	2	16	0	0

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	8		
Units: Participants	8	1		

Statistical analyses

No statistical analyses for this end point

Primary: Cmax - Maximum Observed Serum Concentration

End point title	Cmax - Maximum Observed Serum Concentration[34]

End point description:

One cycle = 4 weeks for Nivolumab
%CV is regular coefficient of variation expressed in percentage (ratio of the sample standard deviation to the sample mean of the original non-transformed data).

End point type	Primary

End point timeframe:

Cycle 1 Day 1 Cycle 2 Day 1

Notes:

[34] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[35]	64[36]	0[37]	0[38]
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	63.238 (± 25.4)	59.024 (± 23.6)	()	()
Cycle 2 Day 1	97.877 (± 24.2)	88.070 (± 25.2)	()	()

Notes:

[35] - Cycle 1 Day 1 n = 12
Cycle 2 Day 1 n = 8
[36] - Cycle 1 Day 1 n = 64
Cycle 2 Day 1 n = 31
[37] - Data not collected.

[38] - Data not collected.

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[39]	0[40]		
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	()	()		

Cycle 2 Day 1	()	()		

Notes:

[39] - Data not collected.

[40] - Data not collected.

Statistical analyses

No statistical analyses for this end point

Primary: AUC(0-T) -Area Under the Concentration-Time Curve from Time Zero to the Last Time of the Last Quantifiable Concentration

End point title	AUC(0-T) -Area Under the Concentration-Time Curve from Time Zero to the Last Time of the Last Quantifiable Concentration[41]

End point description:

One cycle = 4 weeks for Nivolumab
%CV is regular coefficient of variation expressed in percentage (ratio of the sample standard deviation to the sample mean of the original non-transformed data).

End point type	Primary

End point timeframe:

Cycle 1 Day 1 Cycle 2 Day 1

Notes:

[41] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[42]	64[43]	0[44]	0[45]
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	9841.8 (± 28.1)	8078.1 (± 33.9)	()	()
Cycle 2 Day 1	11439.7 (± 29.5)	9524.4 (± 32.3)	()	()

Notes:

[42] - Cycle 1 Day 1 n = 12
Cycle 2 Day 1 n = 8
[43] - Cycle 1 Day 1 n = 64
Cycle 2 Day 1 n = 31
[44] - Data not collected.

[45] - Data not collected.

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[46]	0[47]		
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	()	()		

Cycle 2 Day 1	()	()		

Notes:

[46] - Data not collected.

[47] - Data not collected.

Statistical analyses

No statistical analyses for this end point

Primary: Tmax - Time of Maximum Observed Serum Concentration

End point title	Tmax - Time of Maximum Observed Serum Concentration[48]

End point description:

One cycle = 4 weeks for Nivolumab

End point type	Primary

End point timeframe:

Cycle 1 Day 1 Cycle 2 Day 1

Notes:

[48] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[49]	64[50]	0[51]	0[52]
Units: Hour				
median (full range (min-max))				
Cycle 1 Day 1	1.1420 (1.000 to 1.550)	1.330 (0.967 to 73.317)	(to)	(to)
Cycle 2 Day 1	1.0830 (1.000 to 23.083)	1.1000 (0.867 to 44.917)	(to)	(to)

Notes:

[49] - Cycle 1 Day 1 n = 12
Cycle 2 Day 1 n = 8

[50] - Cycle 1 Day 1 n = 64
Cycle 2 Day 1 n = 31

[51] - Data not collected.

[52] - Data not collected.

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[53]	0[54]		
Units: Hour				
median (full range (min-max))				
Cycle 1 Day 1	(to)	(to)		
Cycle 2 Day 1	(to)	(to)		

Notes:

[53] - Data not collected.

[54] - Data not collected.

Statistical analyses

No statistical analyses for this end point

Primary: CTAU

End point title	CTAU[55]

End point description:

One cycle = 4 weeks for Nivolumab.
%CV is regular coefficient of variation expressed in percentage (ratio of the sample standard deviation to the sample mean of the original non-transformed data).

End point type	Primary

End point timeframe:

Cycle 1 Day 1

Notes:

[55] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	52	0[56]	0[57]
Units: ug/mL				
geometric mean (geometric coefficient of variation)	18.648 (± 34.4)	19.736 (± 26.6)	()	()

Notes:

[56] - Data not collected.

[57] - Data not collected.

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[58]	0[59]		
Units: ug/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[58] - Data not collected.

[59] - Data not collected.

Statistical analyses

No statistical analyses for this end point

Primary: AUC(TAU) - Area Under the Concentration-Time Curve in One Dosing Interval

End point title	AUC(TAU) - Area Under the Concentration-Time Curve in One Dosing Interval[60]

End point description:

One cycle = 4 weeks for Nivolumab.
%CV is regular coefficient of variation expressed in percentage (ratio of the sample standard deviation to the sample mean of the original non-transformed data)

End point type	Primary

End point timeframe:

Cycle 1 Day 1

Notes:

[60] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	53	0[61]	0[62]
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)	9841.8 (± 28.1)	9416.0 (± 22.8)	()	()

Notes:

[61] - Data not collected.

[62] - Data not collected.

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[63]	0[64]		
Units: h*ug/mL				
geometric mean (geometric coefficient of variation)	()	()		

Notes:

[63] - Data not collected.

[64] - Data not collected.

Statistical analyses

No statistical analyses for this end point

Primary: Summary Statistics for Varicella-Zoster V Ab IgG (Index) Titer

End point title	Summary Statistics for Varicella-Zoster V Ab IgG (Index)

End point description:

Summary statistics are measuring the concentration of antibodies in a person's blood sample. All treated subjects with evaluable result at the considered timepoint are included in this analysis. Cases with titer values below detection level or otherwise marked as non-quantifiable considered missing.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[65] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[66]	6	0[67]	1
Units: Index				
median (full range (min-max))	(to)	720.0 (168 to 1225)	(to)	2175.0 (2175 to 2175)

Notes:

[66] - 0 participants with evaluable result at this timepoint

[67] - 0 participants with evaluable result at this timepoint

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	1		
Units: Index				
median (full range (min-max))	813.0 (145 to 2949)	283.0 (283 to 283)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary Statistics for Rubella Antibodies IgG (Index) Titer at Each Timepoint

End point title	Summary Statistics for Rubella Antibodies IgG (Index) Titer at Each Timepoint[68]

End point description:

Summary statistics are measuring the concentration of antibodies in a person's blood sample. All treated subjects with evaluable result at the considered timepoint are included in this analysis. Cases with titer values below detection level or otherwise marked as non-quantifiable considered missing.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[68] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	19	1	5
Units: Index				
median (full range (min-max))	5.810 (1.49 to 7.49)	3.000 (1.05 to 17.70)	15.100 (15.10 to 15.10)	1.810 (0.92 to 9.27)

End point values	Part D: Nivo 3	Part E: Nivo 1		

	mg/kg + Ipi 1 mg/kg	mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	2		
Units: Index				
median (full range (min-max))	2.020 (0.82 to 10.90)	1.605 (1.52 to 1.69)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary Statistics for Rubeola Antibodies IgG (AU/mL) Titer at Each Timepoint

End point title	Summary Statistics for Rubeola Antibodies IgG (AU/mL) Titer at Each Timepoint[69]

End point description:

Summary statistics are measuring the concentration of antibodies in a person's blood sample. All treated subjects with evaluable result at the considered timepoint are included in this analysis. Cases with titer values below detection level or otherwise marked as non-quantifiable considered missing.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[69] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	5	0[70]	2
Units: AU/mL				
median (full range (min-max))	30.40 (30.4 to 30.4)	136.00 (71.7 to 208.0)	(to)	43.10 (32.1 to 54.1)

Notes:

[70] - 0 participants with evaluable result at this timepoint

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: AU/mL				
median (full range (min-max))	105.65 (36.9 to 190.0)	47.90 (47.9 to 47.9)		

Statistical analyses

No statistical analyses for this end point

Primary: Summary Statistics for Mumps Antibodies IgG (AU/mL) Titer at Each Timepoint

End point title	Summary Statistics for Mumps Antibodies IgG (AU/mL) Titer at Each Timepoint[71]

End point description:

Summary statistics are measuring the concentration of antibodies in a person's blood sample. All treated subjects with evaluable result at the considered timepoint are included in this analysis. Cases with titer values below detection level or otherwise marked as non-quantifiable considered missing.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[71] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	18	1	3
Units: AU/mL				
median (full range (min-max))	43.00 (34.1 to 97.1)	56.25 (9.0 to 259.0)	92.20 (92.2 to 92.2)	66.00 (21.3 to 110.0)

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	2		
Units: AU/mL				
median (full range (min-max))	96.80 (13.1 to 235.0)	112.10 (52.2 to 172.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Who Lost Their Positivity/Immune Level for Varicella-Zoster V Ab IgG (Index)

End point title	Number of Subjects Who Lost Their Positivity/Immune Level for Varicella-Zoster V Ab IgG (Index)[72]

End point description:

All treated subjects who had titer above the positivity/immune level at baseline were included in this analysis. Baseline is defined as evaluations or events that occur before the date and time of the first dose of study treatment.

Negative/non-immune: titer is strictly below the detection level 135 Index.
Equivocal: antibody titer is in the ranges [135-165] Index.

Positive/immune: titer is strictly above the positivity/immune level 165 Index.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[72] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[73]	13	2	1
Units: Index				
NEGATIVE/NON-IMMUNE		0	0	0
EQUIVOCAL		0	0	0
POSITIVE/IMMUNE		5	0	0
NOT REPORTED		8	2	1

Notes:

[73] - No participants with Titer Above the Positivity/Immune Level at Baseline

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Index				
NEGATIVE/NON-IMMUNE	0	0		
EQUIVOCAL	1	0		
POSITIVE/IMMUNE	6	2		
NOT REPORTED	3	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Who Lost Their Positivity/Immune Level for Rubella Antibodies IgG (Index)

End point title	Number of Subjects Who Lost Their Positivity/Immune Level for Rubella Antibodies IgG (Index)[74]

End point description:

All treated subjects who had titer above the positivity/immune level at baseline were included in this analysis. Baseline is defined as evaluations or events that occur before the date and time of the first dose of study treatment.

Negative/non-immune: titer is strictly below the detection level 25.0 AU/mL or 13.5 AU/mL.
Equivocal: antibody titer is in the ranges [25.0-29.9] AU/mL or [13.5-16.4] AU/mL.
Positive/immune: titer is strictly above the positivity/immune level 29.9 AU/mL or 16.4 AU/mL.
Different thresholds for Rubeola Antibodies IgG are used for different samples.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[74] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	37	6	7
Units: Participants				
NEGATIVE/NON-IMMUNE	0	0	0	1
EQUIVOCAL	0	0	0	0
POSITIVE/IMMUNE	5	19	1	3
NOT REPORTED	4	18	5	3

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: Participants				
NEGATIVE/NON-IMMUNE	0	0		
EQUIVOCAL	0	0		
POSITIVE/IMMUNE	10	2		
NOT REPORTED	5	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Lost Their Positivity/Immune Level for Rubeola Antibodies IgG (AU/mL)

End point title	Number of Participants Who Lost Their Positivity/Immune Level for Rubeola Antibodies IgG (AU/mL)[75]

End point description:

All treated subjects who had titer above the positivity/immune level at baseline were included in this analysis. Baseline is defined as evaluations or events that occur before the date and time of the first dose of study treatment.

Negative/non-immune: titer is strictly below the detection level 25.0 AU/mL or 13.5 AU/mL.
Equivocal: antibody titer is in the ranges [25.0-29.9] AU/mL or [13.5-16.4] AU/mL.
Positive/immune: titer is strictly above the positivity/immune level 29.9 AU/mL or 16.4 AU/mL.
Different thresholds for Rubeola Antibodies IgG are used for different samples.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[75] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	19	1	1
Units: Participants				
NEGATIVE/NON-IMMUNE	0	1	0	0
EQUIVOCAL	0	0	0	0
POSITIVE/IMMUNE	0	6	0	0
NOT REPORTED	1	12	1	1

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: Participants				
NEGATIVE/NON-IMMUNE	1	0		
EQUIVOCAL	0	0		
POSITIVE/IMMUNE	6	2		
NOT REPORTED	3	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Who Lost Their Positivity/Immune Level for Mumps Antibodies IgG (AU/mL)

End point title	Number of Subjects Who Lost Their Positivity/Immune Level for Mumps Antibodies IgG (AU/mL)[76]

End point description:

All treated subjects who had titer above the positivity/immune level at baseline were included in this analysis. Baseline is defined as evaluations or events that occur before the date and time of the first dose of study treatment.

Negative/non-immune: titer is strictly below the detection level 9.0 AU/mL.
Equivocal: antibody titer is in the ranges [9.0-10.9] AU/mL.
Positive/immune: titer is strictly above the positivity/immune level 10.9 AU/mL.

End point type	Primary

End point timeframe:

Cycle 2 Day 1

Notes:

[76] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	35	5	7
Units: Participants				
NEGATIVE/NON-IMMUNE	0	0	0	0
EQUIVOCAL	0	1	0	0
POSITIVE/IMMUNE	4	18	1	3
NOT REPORTED	4	16	4	4

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	3		
Units: Participants				
NEGATIVE/NON-IMMUNE	0	0		
EQUIVOCAL	0	0		
POSITIVE/IMMUNE	10	2		
NOT REPORTED	4	1		

Statistical analyses

No statistical analyses for this end point

Primary: The Number of Participants with Antidrug Antibody (ADA) Measurements (Nivolumab)

End point title	The Number of Participants with Antidrug Antibody (ADA) Measurements (Nivolumab)[77]

End point description:

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or
ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment.
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.

End point type	Primary

End point timeframe:

In Parts A and B, serum samples were collected prior to Day 1 nivolumab infusion in each cycle. In Parts C and D, serum samples were collected prior to Day 1 nivolumab infusion in each cycle for ADA assessment of both Nivolumab and Ipilimumab.

Notes:

[77] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	41	2	9
Units: Participants				
BASELINE ADA POSITIVE	1	2	0	1
ADA POSITIVE	0	1	1	0
NEUTRALIZING POSITIVE	0	0	0	0
ADA NEGATIVE	10	40	1	9

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	6		
Units: Participants				
BASELINE ADA POSITIVE	1	0		
ADA POSITIVE	0	0		
NEUTRALIZING POSITIVE	0	0		
ADA NEGATIVE	24	6		

Statistical analyses

No statistical analyses for this end point

Primary: The Number of Participants with Antidrug Antibody (ADA) Measurements (Ipilimumab)

End point title	The Number of Participants with Antidrug Antibody (ADA) Measurements (Ipilimumab)[78][79]

End point description:

Baseline ADA Positive: A subject with baseline ADA-positive sample;
ADA Positive: A subject with at least one ADA-positive sample relative to baseline (ADA negative at baseline or
ADA titer to be at least 4-fold or greater (>=) than baseline positive titer) at any time after initiation of treatment.
Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected post-baseline;
ADA Negative: A subject with no ADA-positive sample after initiation of treatment.

End point type	Primary

End point timeframe:

In Parts A and B, serum samples were collected prior to Day 1 nivolumab infusion in each cycle. In Parts C and D, serum samples were collected prior to Day 1 nivolumab infusion in each cycle for ADA assessment of both Nivolumab and Ipilimumab.

Notes:

[78] - 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: Only summary statistics planned for this endpoint

[79] - 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: Endpoint is specific to only certain study arms

End point values	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	8	23	6
Units: Participants				
BASELINE ADA POSITIVE	0	1	0	0
ADA POSITIVE	0	0	0	0
NEUTRALIZING POSITIVE	0	0	0	0
ADA NEGATIVE	2	8	23	6

Statistical analyses

No statistical analyses for this end point

Primary: Biomarker Expression Analysis of Nivolumab as a Singel Agent or in Combination with Ipilimumab

End point title	Biomarker Expression Analysis of Nivolumab as a Singel Agent or in Combination with Ipilimumab[80]

End point description:

Data were not and will never be collected.

End point type	Primary

End point timeframe:

Cycle 1 (21 days)

Notes:

[80] - 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: Only summary statistics planned for this endpoint

End point values	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[81]	0[82]	0[83]	0[84]
Units: Participants				

Notes:

[81] - Data were not and will never be collected.

[82] - Data were not and will never be collected.

[83] - Data were not and will never be collected.

[84] - Data were not and will never be collected.

End point values	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[85]	0[86]		
Units: Participants				

Notes:

[85] - Data were not and will never be collected.

[86] - Data were not and will never be collected.

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs were assessed from first dose to 100 days after last dose of study therapy (up to approximately 63 months)

Adverse event reporting additional description:

The below Non-Serious AEs could not be coded therefore have been categorized as "unassigned" and are outlined below:

Reported below are the # of subjects affected (#A) and the # of occurrences (all) (#O).

Part A: (#A=2) (#O=2)
Part B: (#A=8) (#O=13)
Part C1: (#A=0) (#O=0)
Part C2: (#A=2) (#O=2)
Part D: (#A=2) (#O=2)
Part E: (#A=4) (#O=6)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Part A: Nivo 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days. A1: Recurrent or refractory solid tumors, without CNS tumors or known CNS metastases.

Reporting group title	Part B: Nivo 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg Q2 week IV. A cycle was considered 28 days.

B1: Relapsed or refractory neuroblastoma
B2: Relapsed or refractory osteosarcoma
B3: Relapsed or refractory rhabdomyosarcoma
B4: Relapsed or refractory Ewing sarcoma or Peripheral PNET
B5: Relapsed or refractory Hodgkin Lymphoma
B6: Relapsed or refractory non-Hodgkin Lymphoma
B7: Unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma
B8: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

Reporting group title	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part E; in cycle 5 and for subsequent cycles, cycle length was 28 days and nivolumab 3 mg/kg was to be administered on days 1 and 15 of each cycle.

E3: Relapsed or refractory rhabdomyosarcoma
E4: Relapsed or refractory Ewing Sarcoma or Peripheral PNET

Reporting group title	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C2: Recurrent or refractory solid tumors, without CNS tumors or known CNS metastases.

Reporting group title	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part D, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

D1: Relapsed or refractory neuroblastoma
D2: Relapsed or refractory osteosarcoma
D3: Relapsed or refractory rhabdomyosarcoma
D4: Relapsed or refractory Ewing Sarcoma or Peripheral PNET
D5: Relapsed or refractory non-Hodgkin Lymphoma
D6: Relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease)

Reporting group title	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg

Reporting group description:

Participants in the below cohorts receive nivolumab 1 mg/kg + ipilimumab 1 mg/kg Q3 week x 4 followed by nivolumab 3 mg/kg Q2 week IV. Note that cycle length was 21 days for the first 4 cycles of Part C, whereas reverted to 28 days for subsequent cycles which comprised two doses of nivolumab, and was the same regimen used in Part A and B.

C1: Recurrent or refractory solid tumors, without CNS tumors or known CNS metastases.

Serious adverse events	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	39 / 68 (57.35%)	6 / 8 (75.00%)
number of deaths (all causes)	6	38	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 12 (8.33%)	7 / 68 (10.29%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Haematoma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Haemorrhage			

subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
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	1 / 12 (8.33%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 12 (16.67%)	14 / 68 (20.59%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 2	0 / 14	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 14	0 / 1
Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (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
Pyrexia			
subjects affected / exposed	3 / 12 (25.00%)	10 / 68 (14.71%)	2 / 8 (25.00%)
occurrences causally related to treatment / all	1 / 3	4 / 11	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Immune system disorders			

Autoimmune disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Cytokine release syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Oedema genital			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			

subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Laryngeal oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (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
Haemothorax			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	3 / 12 (25.00%)	4 / 68 (5.88%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	1 / 3	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Pneumonitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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

Lipase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			

subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Ventricular fibrillation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
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 arrest			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Ventricular arrhythmia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical cord compression			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Headache			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Nervous system disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Spinal cord compression			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Seizure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Phantom limb syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Syncope			

subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
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 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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

Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			

subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Pollakiuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Nephrolithiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Urinary tract obstruction			

subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Urinary retention			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
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			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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

Flank pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Sepsis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
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	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (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
Periorbital cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
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 infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Hypermagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)	15 / 28 (53.57%)	3 / 6 (50.00%)
number of deaths (all causes)	8	18	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Vascular disorders			
Embolism			

subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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
Haematoma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (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
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Disease progression			
subjects affected / exposed	0 / 12 (0.00%)	6 / 28 (21.43%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 6	0 / 0
Chills			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Pyrexia			

subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 system disorders			
Autoimmune disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytokine release syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 genital			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Cough			

subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Hypoxia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	5 / 28 (17.86%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	3 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Tachypnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			

subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Ventricular fibrillation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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

Pericardial effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Encephalopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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
Cervical cord compression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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
Presyncope			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phantom limb syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Eye swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Duodenitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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

Ascites			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Anal fistula			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			

subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Large intestinal obstruction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Rash maculo-papular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 colic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pollakiuria			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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
Urinary retention			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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			
Hyperthyroidism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (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
Device related infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
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 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Skin infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypermagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (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

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

Non-serious adverse events	Part A: Nivo 3 mg/kg	Part B: Nivo 3 mg/kg	Part E: Nivo 1 mg/kg + Ipi 3 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	68 / 68 (100.00%)	8 / 8 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	1 / 8 (12.50%)
occurrences (all)	0	5	1
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	11 / 68 (16.18%)	3 / 8 (37.50%)
occurrences (all)	1	20	4
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Hypertension			
subjects affected / exposed	6 / 12 (50.00%)	13 / 68 (19.12%)	2 / 8 (25.00%)
occurrences (all)	12	24	2
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 12 (16.67%)	5 / 68 (7.35%)	2 / 8 (25.00%)
occurrences (all)	2	5	3
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	1 / 8 (12.50%)
occurrences (all)	0	5	1
Facial pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Fatigue			
subjects affected / exposed	8 / 12 (66.67%)	41 / 68 (60.29%)	7 / 8 (87.50%)
occurrences (all)	10	49	8
Gait disturbance			
subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	1	4	1
Influenza like illness			

subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences (all)	0	4	1
Localised oedema			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Face oedema			
subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	1	5	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 12 (0.00%)	8 / 68 (11.76%)	4 / 8 (50.00%)
occurrences (all)	0	8	6
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)	8 / 68 (11.76%)	2 / 8 (25.00%)
occurrences (all)	2	8	2
Pain			
subjects affected / exposed	4 / 12 (33.33%)	16 / 68 (23.53%)	1 / 8 (12.50%)
occurrences (all)	5	17	2
Pyrexia			
subjects affected / exposed	3 / 12 (25.00%)	26 / 68 (38.24%)	3 / 8 (37.50%)
occurrences (all)	5	34	4
Swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Pelvic pain			

subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Penile pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	4 / 12 (33.33%)	9 / 68 (13.24%)	1 / 8 (12.50%)
occurrences (all)	4	9	2
Dyspnoea			
subjects affected / exposed	3 / 12 (25.00%)	13 / 68 (19.12%)	4 / 8 (50.00%)
occurrences (all)	3	17	6
Dysphonia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	2	1	1
Cough			
subjects affected / exposed	8 / 12 (66.67%)	26 / 68 (38.24%)	4 / 8 (50.00%)
occurrences (all)	11	36	5
Atelectasis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Pneumothorax			
subjects affected / exposed	2 / 12 (16.67%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)	6 / 68 (8.82%)	1 / 8 (12.50%)
occurrences (all)	1	7	1
Nasal congestion			
subjects affected / exposed	3 / 12 (25.00%)	15 / 68 (22.06%)	3 / 8 (37.50%)
occurrences (all)	5	20	3
Oropharyngeal pain			
subjects affected / exposed	2 / 12 (16.67%)	7 / 68 (10.29%)	2 / 8 (25.00%)
occurrences (all)	2	7	3
Oropharyngeal plaque			

subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	4 / 68 (5.88%)	2 / 8 (25.00%)
occurrences (all)	0	4	2
Pneumonitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Hiccups			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tachypnoea			
subjects affected / exposed	1 / 12 (8.33%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	1	6	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sinus pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 12 (16.67%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	3	4	1
Rhinitis allergic			
subjects affected / exposed	2 / 12 (16.67%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	2	6	0
Productive cough			
subjects affected / exposed	0 / 12 (0.00%)	6 / 68 (8.82%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Throat irritation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Wheezing			
subjects affected / exposed	1 / 12 (8.33%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	1	16	0
Upper-airway cough syndrome			

subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	12 / 68 (17.65%)	3 / 8 (37.50%)
occurrences (all)	0	12	3
Hallucination			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Depression			
subjects affected / exposed	2 / 12 (16.67%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	2	5	0
Delirium			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	1 / 12 (8.33%)	3 / 68 (4.41%)	1 / 8 (12.50%)
occurrences (all)	1	3	1
Personality change			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Agitation			
subjects affected / exposed	2 / 12 (16.67%)	1 / 68 (1.47%)	2 / 8 (25.00%)
occurrences (all)	2	1	2
Irritability			
subjects affected / exposed	1 / 12 (8.33%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	1	7	0
Anxiety			
subjects affected / exposed	4 / 12 (33.33%)	12 / 68 (17.65%)	0 / 8 (0.00%)
occurrences (all)	5	12	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 12 (8.33%)	9 / 68 (13.24%)	1 / 8 (12.50%)
occurrences (all)	1	10	1
Activated partial thromboplastin time shortened			

subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood bicarbonate decreased			
subjects affected / exposed	1 / 12 (8.33%)	6 / 68 (8.82%)	3 / 8 (37.50%)
occurrences (all)	1	7	3
Alanine aminotransferase increased			
subjects affected / exposed	5 / 12 (41.67%)	29 / 68 (42.65%)	4 / 8 (50.00%)
occurrences (all)	6	39	4
Amylase decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	1 / 8 (12.50%)
occurrences (all)	0	5	1
Anion gap increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 12 (50.00%)	30 / 68 (44.12%)	7 / 8 (87.50%)
occurrences (all)	7	50	7
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 12 (16.67%)	15 / 68 (22.06%)	2 / 8 (25.00%)
occurrences (all)	3	19	2
Alanine aminotransferase decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood bicarbonate increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			
subjects affected / exposed	1 / 12 (8.33%)	11 / 68 (16.18%)	2 / 8 (25.00%)
occurrences (all)	1	12	2
Blood chloride decreased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	3	0

Blood cholesterol increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Blood creatinine decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	3 / 12 (25.00%)	20 / 68 (29.41%)	3 / 8 (37.50%)
occurrences (all)	7	31	3
Carbon dioxide decreased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 12 (16.67%)	3 / 68 (4.41%)	1 / 8 (12.50%)
occurrences (all)	3	4	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 12 (16.67%)	4 / 68 (5.88%)	2 / 8 (25.00%)
occurrences (all)	3	5	2
Blood urea decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	4	0
C-reactive protein			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	0	9	0
C-reactive protein increased			
subjects affected / exposed	2 / 12 (16.67%)	17 / 68 (25.00%)	0 / 8 (0.00%)
occurrences (all)	2	22	0
Blood fibrinogen decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 12 (0.00%)	4 / 68 (5.88%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	1	4	1
Haemoglobin increased			
subjects affected / exposed	2 / 12 (16.67%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	2	11	0
International normalised ratio increased			
subjects affected / exposed	0 / 12 (0.00%)	6 / 68 (8.82%)	1 / 8 (12.50%)
occurrences (all)	0	6	1
Lipase increased			
subjects affected / exposed	1 / 12 (8.33%)	5 / 68 (7.35%)	2 / 8 (25.00%)
occurrences (all)	1	15	2
Lymphocyte count decreased			
subjects affected / exposed	9 / 12 (75.00%)	40 / 68 (58.82%)	7 / 8 (87.50%)
occurrences (all)	13	88	9
Lymphocyte count increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Neutrophil count decreased			
subjects affected / exposed	7 / 12 (58.33%)	36 / 68 (52.94%)	3 / 8 (37.50%)
occurrences (all)	11	103	4
Platelet count decreased			
subjects affected / exposed	7 / 12 (58.33%)	40 / 68 (58.82%)	3 / 8 (37.50%)
occurrences (all)	11	90	3
Protein total decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Thyroxine free decreased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Urine output decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	4 / 12 (33.33%)	15 / 68 (22.06%)	3 / 8 (37.50%)
occurrences (all)	4	17	3
Weight increased			
subjects affected / exposed	2 / 12 (16.67%)	5 / 68 (7.35%)	2 / 8 (25.00%)
occurrences (all)	2	5	2
White blood cell count decreased			
subjects affected / exposed	7 / 12 (58.33%)	41 / 68 (60.29%)	4 / 8 (50.00%)
occurrences (all)	17	113	5
White blood cell count increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	2 / 12 (16.67%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	2	3	0
Arthropod bite			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Contusion			
subjects affected / exposed	1 / 12 (8.33%)	6 / 68 (8.82%)	0 / 8 (0.00%)
occurrences (all)	1	6	0
Fall			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	2 / 8 (25.00%)
occurrences (all)	1	1	2
Fracture			
subjects affected / exposed	0 / 12 (0.00%)	4 / 68 (5.88%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Infusion related reaction			

subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	1	4	1
Seroma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Vascular access complication			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Wound complication			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sinus bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	0	5	0
Sinus tachycardia			
subjects affected / exposed	6 / 12 (50.00%)	26 / 68 (38.24%)	3 / 8 (37.50%)
occurrences (all)	13	31	5
Supraventricular extrasystoles			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pericardial effusion			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Amnesia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Depressed level of consciousness			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)	8 / 68 (11.76%)	2 / 8 (25.00%)
occurrences (all)	1	8	2
Dysgeusia			
subjects affected / exposed	1 / 12 (8.33%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Seizure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Radiculopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Phantom limb syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 12 (8.33%)	5 / 68 (7.35%)	1 / 8 (12.50%)
occurrences (all)	1	5	1
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	6 / 68 (8.82%)	0 / 8 (0.00%)
occurrences (all)	0	6	0
Lethargy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypersomnia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hemiparesis			

subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	4 / 12 (33.33%)	21 / 68 (30.88%)	3 / 8 (37.50%)
occurrences (all)	6	25	3
Encephalopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dyskinesia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Trigeminal nerve disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	2
Somnolence			
subjects affected / exposed	2 / 12 (16.67%)	6 / 68 (8.82%)	0 / 8 (0.00%)
occurrences (all)	2	6	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 12 (91.67%)	51 / 68 (75.00%)	4 / 8 (50.00%)
occurrences (all)	21	81	7
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eosinophilia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	3 / 8 (37.50%)
occurrences (all)	0	1	3
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	0	5	0
Ear and labyrinth disorders			

External ear pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Hypoacusis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Eye disorders			
Anisocoria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Diplopia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Photopsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	1 / 12 (8.33%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Eyelid function disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eyelid margin crusting			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Periorbital oedema			
subjects affected / exposed	2 / 12 (16.67%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	2	2	0
Photophobia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Eye disorder			

subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Uveitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 12 (0.00%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	0	4	1
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Vitreous floaters			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	2 / 8 (25.00%)
occurrences (all)	0	6	2
Abdominal pain			
subjects affected / exposed	3 / 12 (25.00%)	21 / 68 (30.88%)	5 / 8 (62.50%)
occurrences (all)	3	27	7
Duodenal ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Anal incontinence			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ascites			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	6 / 12 (50.00%)	24 / 68 (35.29%)	3 / 8 (37.50%)
occurrences (all)	6	28	3

Diarrhoea			
subjects affected / exposed	3 / 12 (25.00%)	17 / 68 (25.00%)	4 / 8 (50.00%)
occurrences (all)	7	26	4
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)	5 / 68 (7.35%)	0 / 8 (0.00%)
occurrences (all)	1	6	0
Dysphagia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	2	1	0
Eructation			
subjects affected / exposed	2 / 12 (16.67%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Flatulence			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Gastritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Oral pain			
subjects affected / exposed	1 / 12 (8.33%)	3 / 68 (4.41%)	1 / 8 (12.50%)
occurrences (all)	1	3	1
Lip disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mouth haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	0	2	0

Nausea			
subjects affected / exposed	6 / 12 (50.00%)	32 / 68 (47.06%)	3 / 8 (37.50%)
occurrences (all)	8	43	3
Oesophageal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Oesophagitis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Gingival pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pancreatitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	1	4	1
Toothache			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	4 / 12 (33.33%)	32 / 68 (47.06%)	4 / 8 (50.00%)
occurrences (all)	5	50	4
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 12 (16.67%)	6 / 68 (8.82%)	1 / 8 (12.50%)
occurrences (all)	2	7	1
Dermatitis contact			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	2 / 8 (25.00%)
occurrences (all)	0	5	2
Blister			

subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)	5 / 68 (7.35%)	1 / 8 (12.50%)
occurrences (all)	1	5	1
Erythema			
subjects affected / exposed	1 / 12 (8.33%)	6 / 68 (8.82%)	0 / 8 (0.00%)
occurrences (all)	1	6	0
Pain of skin			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Pruritus			
subjects affected / exposed	5 / 12 (41.67%)	12 / 68 (17.65%)	2 / 8 (25.00%)
occurrences (all)	5	13	3
Rash			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash macular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urticaria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Skin exfoliation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Rash maculo-papular			

subjects affected / exposed	5 / 12 (41.67%)	11 / 68 (16.18%)	1 / 8 (12.50%)
occurrences (all)	5	14	1
Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Acute kidney injury			
subjects affected / exposed	0 / 12 (0.00%)	4 / 68 (5.88%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Chromaturia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Glycosuria			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Haematuria			
subjects affected / exposed	4 / 12 (33.33%)	13 / 68 (19.12%)	3 / 8 (37.50%)
occurrences (all)	6	16	4
Haemoglobinuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ketonuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Micturition urgency			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	2 / 8 (25.00%)
occurrences (all)	0	4	2
Proteinuria			
subjects affected / exposed	1 / 12 (8.33%)	14 / 68 (20.59%)	4 / 8 (50.00%)
occurrences (all)	1	15	5
Urinary incontinence			
subjects affected / exposed	1 / 12 (8.33%)	4 / 68 (5.88%)	1 / 8 (12.50%)
occurrences (all)	1	4	1
Urinary retention			
subjects affected / exposed	0 / 12 (0.00%)	9 / 68 (13.24%)	0 / 8 (0.00%)
occurrences (all)	0	10	0

Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Endocrine disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hyperthyroidism			
subjects affected / exposed	0 / 12 (0.00%)	7 / 68 (10.29%)	2 / 8 (25.00%)
occurrences (all)	0	8	2
Hypothyroidism			
subjects affected / exposed	2 / 12 (16.67%)	10 / 68 (14.71%)	2 / 8 (25.00%)
occurrences (all)	2	10	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	18 / 68 (26.47%)	1 / 8 (12.50%)
occurrences (all)	0	19	1
Arthralgia			
subjects affected / exposed	1 / 12 (8.33%)	6 / 68 (8.82%)	3 / 8 (37.50%)
occurrences (all)	1	6	3
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	23 / 68 (33.82%)	1 / 8 (12.50%)
occurrences (all)	2	29	1
Neck pain			
subjects affected / exposed	1 / 12 (8.33%)	3 / 68 (4.41%)	1 / 8 (12.50%)
occurrences (all)	1	3	1
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	2 / 8 (25.00%)
occurrences (all)	0	5	2
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			

subjects affected / exposed	0 / 12 (0.00%)	11 / 68 (16.18%)	2 / 8 (25.00%)
occurrences (all)	0	11	2
Muscle spasms			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	1	1	1
Joint range of motion decreased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Flank pain			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	1 / 8 (12.50%)
occurrences (all)	0	6	1
Chest wall mass			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	5 / 68 (7.35%)	1 / 8 (12.50%)
occurrences (all)	0	5	1
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 12 (8.33%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	0	4	0
Device related infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Mucosal infection			
subjects affected / exposed	1 / 12 (8.33%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	1	3	0
Oral candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0

Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	6 / 68 (8.82%)	0 / 8 (0.00%)
occurrences (all)	0	8	0
Rash pustular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Skin infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	8 / 68 (11.76%)	1 / 8 (12.50%)
occurrences (all)	1	16	1
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	4 / 68 (5.88%)	2 / 8 (25.00%)
occurrences (all)	0	6	3
Wound infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 68 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Alkalosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyperphosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)	8 / 68 (11.76%)	1 / 8 (12.50%)
occurrences (all)	1	9	1
Hypercalcaemia			

subjects affected / exposed	1 / 12 (8.33%)	7 / 68 (10.29%)	0 / 8 (0.00%)
occurrences (all)	1	7	0
Hyperglycaemia			
subjects affected / exposed	5 / 12 (41.67%)	27 / 68 (39.71%)	7 / 8 (87.50%)
occurrences (all)	8	36	9
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	15 / 68 (22.06%)	1 / 8 (12.50%)
occurrences (all)	1	15	1
Hypermagnesaemia			
subjects affected / exposed	2 / 12 (16.67%)	13 / 68 (19.12%)	0 / 8 (0.00%)
occurrences (all)	2	21	0
Hypernatraemia			
subjects affected / exposed	0 / 12 (0.00%)	7 / 68 (10.29%)	0 / 8 (0.00%)
occurrences (all)	0	11	0
Decreased appetite			
subjects affected / exposed	4 / 12 (33.33%)	25 / 68 (36.76%)	4 / 8 (50.00%)
occurrences (all)	4	29	5
Vitamin D deficiency			
subjects affected / exposed	1 / 12 (8.33%)	1 / 68 (1.47%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Hypophosphataemia			
subjects affected / exposed	4 / 12 (33.33%)	28 / 68 (41.18%)	3 / 8 (37.50%)
occurrences (all)	6	34	4
Hyponatraemia			
subjects affected / exposed	7 / 12 (58.33%)	37 / 68 (54.41%)	4 / 8 (50.00%)
occurrences (all)	8	54	6
Hypomagnesaemia			
subjects affected / exposed	0 / 12 (0.00%)	22 / 68 (32.35%)	3 / 8 (37.50%)
occurrences (all)	0	29	3
Hypertriglyceridaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 68 (1.47%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Hypoglycaemia			
subjects affected / exposed	2 / 12 (16.67%)	9 / 68 (13.24%)	2 / 8 (25.00%)
occurrences (all)	4	9	2
Hypochloraemia			

subjects affected / exposed	3 / 12 (25.00%)	3 / 68 (4.41%)	0 / 8 (0.00%)
occurrences (all)	3	4	0
Hypocalcaemia			
subjects affected / exposed	6 / 12 (50.00%)	34 / 68 (50.00%)	6 / 8 (75.00%)
occurrences (all)	6	53	8
Hypoalbuminaemia			
subjects affected / exposed	6 / 12 (50.00%)	36 / 68 (52.94%)	6 / 8 (75.00%)
occurrences (all)	6	45	7
Hyperuricaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 68 (2.94%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Hypokalaemia			
subjects affected / exposed	6 / 12 (50.00%)	26 / 68 (38.24%)	3 / 8 (37.50%)
occurrences (all)	8	39	5

Non-serious adverse events	Part C2: Nivo 3 mg/kg + Ipi 1 mg/kg	Part D: Nivo 3 mg/kg + Ipi 1 mg/kg	Part C1: Nivo 1 mg/kg + Ipi 1 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	28 / 28 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	2 / 6 (33.33%)
occurrences (all)	0	3	2
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 12 (8.33%)	7 / 28 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	17	0
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	2 / 12 (16.67%)	11 / 28 (39.29%)	1 / 6 (16.67%)
occurrences (all)	3	25	1
General disorders and administration site conditions			
Chills			

subjects affected / exposed	1 / 12 (8.33%)	6 / 28 (21.43%)	0 / 6 (0.00%)
occurrences (all)	1	6	0
Malaise			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Facial pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	6 / 12 (50.00%)	16 / 28 (57.14%)	2 / 6 (33.33%)
occurrences (all)	6	21	2
Gait disturbance			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Influenza like illness			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Localised oedema			
subjects affected / exposed	0 / 12 (0.00%)	4 / 28 (14.29%)	2 / 6 (33.33%)
occurrences (all)	0	4	3
Face oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	2 / 12 (16.67%)	6 / 28 (21.43%)	1 / 6 (16.67%)
occurrences (all)	2	6	1
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	6 / 28 (21.43%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Pain			
subjects affected / exposed	2 / 12 (16.67%)	4 / 28 (14.29%)	0 / 6 (0.00%)
occurrences (all)	2	5	0
Pyrexia			
subjects affected / exposed	4 / 12 (33.33%)	12 / 28 (42.86%)	2 / 6 (33.33%)
occurrences (all)	8	16	2
Swelling			

subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Pelvic pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Penile pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	7 / 28 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	7	0
Dysphonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	4 / 12 (33.33%)	15 / 28 (53.57%)	2 / 6 (33.33%)
occurrences (all)	4	18	3
Atelectasis			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Pneumothorax			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Nasal congestion			
subjects affected / exposed	1 / 12 (8.33%)	7 / 28 (25.00%)	1 / 6 (16.67%)
occurrences (all)	1	7	1
Oropharyngeal pain			
subjects affected / exposed	2 / 12 (16.67%)	5 / 28 (17.86%)	0 / 6 (0.00%)
occurrences (all)	2	7	0
Oropharyngeal plaque			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)	6 / 28 (21.43%)	0 / 6 (0.00%)
occurrences (all)	1	6	0
Pneumonitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Hiccups			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Tachypnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sinus pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Rhinitis allergic			

subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	2 / 6 (33.33%)
occurrences (all)	0	2	2
Productive cough			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Throat irritation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	1	4	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	6 / 28 (21.43%)	0 / 6 (0.00%)
occurrences (all)	1	6	0
Hallucination			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Delirium			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Confusional state			
subjects affected / exposed	2 / 12 (16.67%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Personality change			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Agitation			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0

Irritability			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	1 / 6 (16.67%)
occurrences (all)	1	3	1
Anxiety			
subjects affected / exposed	3 / 12 (25.00%)	9 / 28 (32.14%)	1 / 6 (16.67%)
occurrences (all)	5	9	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 12 (0.00%)	5 / 28 (17.86%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
Activated partial thromboplastin time shortened			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bicarbonate decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 12 (33.33%)	10 / 28 (35.71%)	3 / 6 (50.00%)
occurrences (all)	5	10	4
Amylase decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Amylase increased			
subjects affected / exposed	5 / 12 (41.67%)	2 / 28 (7.14%)	1 / 6 (16.67%)
occurrences (all)	5	2	1
Anion gap increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 12 (41.67%)	7 / 28 (25.00%)	1 / 6 (16.67%)
occurrences (all)	7	7	1
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 12 (25.00%)	6 / 28 (21.43%)	2 / 6 (33.33%)
occurrences (all)	4	6	2
Alanine aminotransferase decreased			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood bicarbonate increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	2	4	0
Blood chloride decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Blood cholesterol increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Blood creatinine decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	3 / 12 (25.00%)	9 / 28 (32.14%)	3 / 6 (50.00%)
occurrences (all)	5	10	4
Carbon dioxide decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blood urea decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood urea increased			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
C-reactive protein			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	2 / 12 (16.67%)	8 / 28 (28.57%)	1 / 6 (16.67%)
occurrences (all)	2	9	1
Blood fibrinogen decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Haemoglobin increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
International normalised ratio increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Lipase increased			
subjects affected / exposed	3 / 12 (25.00%)	7 / 28 (25.00%)	0 / 6 (0.00%)
occurrences (all)	4	8	0
Lymphocyte count decreased			
subjects affected / exposed	5 / 12 (41.67%)	20 / 28 (71.43%)	3 / 6 (50.00%)
occurrences (all)	6	39	3
Lymphocyte count increased			

subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	4 / 12 (33.33%)	6 / 28 (21.43%)	1 / 6 (16.67%)
occurrences (all)	7	15	2
Platelet count decreased			
subjects affected / exposed	6 / 12 (50.00%)	8 / 28 (28.57%)	3 / 6 (50.00%)
occurrences (all)	6	15	3
Protein total decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Thyroxine free decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urine output decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	4 / 12 (33.33%)	10 / 28 (35.71%)	3 / 6 (50.00%)
occurrences (all)	4	10	3
Weight increased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
White blood cell count decreased			
subjects affected / exposed	5 / 12 (41.67%)	8 / 28 (28.57%)	1 / 6 (16.67%)
occurrences (all)	9	21	2
White blood cell count increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Arthropod bite			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
Fall			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Seroma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin abrasion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Vascular access complication			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Wound complication			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Sinus tachycardia			
subjects affected / exposed	4 / 12 (33.33%)	16 / 28 (57.14%)	2 / 6 (33.33%)
occurrences (all)	4	25	2

Supraventricular extrasystoles			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Amnesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Depressed level of consciousness			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Radiculopathy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Phantom limb syndrome			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hypersomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hemiparesis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	5 / 12 (41.67%)	10 / 28 (35.71%)	3 / 6 (50.00%)
occurrences (all)	5	10	3
Encephalopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dyskinesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Trigeminal nerve disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	1 / 6 (16.67%)
occurrences (all)	1	4	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 12 (100.00%)	17 / 28 (60.71%)	3 / 6 (50.00%)
occurrences (all)	17	22	4

Disseminated intravascular coagulation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eosinophilia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Febrile neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
External ear pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Anisocoria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Photopsia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Eyelid function disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eyelid margin crusting			

subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Periorbital oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Eye disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vision blurred			
subjects affected / exposed	1 / 12 (8.33%)	5 / 28 (17.86%)	1 / 6 (16.67%)
occurrences (all)	1	5	1
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vitreous floaters			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	4 / 28 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Abdominal pain			
subjects affected / exposed	3 / 12 (25.00%)	8 / 28 (28.57%)	1 / 6 (16.67%)
occurrences (all)	3	8	2
Duodenal ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Anal incontinence			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0

Ascites			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	2 / 12 (16.67%)	8 / 28 (28.57%)	2 / 6 (33.33%)
occurrences (all)	2	8	2
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	8 / 28 (28.57%)	1 / 6 (16.67%)
occurrences (all)	1	13	1
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	6 / 28 (21.43%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Abdominal pain upper			
subjects affected / exposed	2 / 12 (16.67%)	5 / 28 (17.86%)	0 / 6 (0.00%)
occurrences (all)	2	5	0
Dysphagia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eructation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	0	4	0

Oral pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Lip disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mouth haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	3 / 12 (25.00%)	12 / 28 (42.86%)	1 / 6 (16.67%)
occurrences (all)	3	14	2
Oesophageal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	2 / 12 (16.67%)	14 / 28 (50.00%)	2 / 6 (33.33%)
occurrences (all)	2	15	2
Skin and subcutaneous tissue disorders			
Dry skin			

subjects affected / exposed	0 / 12 (0.00%)	5 / 28 (17.86%)	0 / 6 (0.00%)
occurrences (all)	0	6	0
Dermatitis contact			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Blister			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	4 / 28 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	4	0
Rash			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Rash erythematous			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash macular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			

subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Skin exfoliation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	2 / 12 (16.67%)	3 / 28 (10.71%)	3 / 6 (50.00%)
occurrences (all)	2	3	4
Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Chromaturia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Glycosuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	1	5	0
Haemoglobinuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Ketonuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Proteinuria			
subjects affected / exposed	6 / 12 (50.00%)	7 / 28 (25.00%)	1 / 6 (16.67%)
occurrences (all)	7	7	1
Urinary incontinence			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Urinary retention			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Endocrine disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperthyroidism			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Hypothyroidism			
subjects affected / exposed	4 / 12 (33.33%)	5 / 28 (17.86%)	0 / 6 (0.00%)
occurrences (all)	4	5	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 12 (16.67%)	9 / 28 (32.14%)	1 / 6 (16.67%)
occurrences (all)	2	11	1
Arthralgia			
subjects affected / exposed	4 / 12 (33.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	4	1	0
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	10 / 28 (35.71%)	1 / 6 (16.67%)
occurrences (all)	2	13	2
Neck pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Myalgia			

subjects affected / exposed	3 / 12 (25.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Musculoskeletal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 12 (16.67%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)	7 / 28 (25.00%)	0 / 6 (0.00%)
occurrences (all)	1	7	0
Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Joint range of motion decreased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
Flank pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Chest wall mass			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Infections and infestations			
Otitis media			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Device related infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mucosal infection			
subjects affected / exposed	1 / 12 (8.33%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	1	2	0
Oral candidiasis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Rash pustular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Skin infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	5 / 28 (17.86%)	1 / 6 (16.67%)
occurrences (all)	0	5	1
Urinary tract infection			
subjects affected / exposed	2 / 12 (16.67%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Wound infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Alkalosis			

subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Hyperphosphataemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	7 / 28 (25.00%)	2 / 6 (33.33%)
occurrences (all)	0	8	2
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Hyperglycaemia			
subjects affected / exposed	5 / 12 (41.67%)	9 / 28 (32.14%)	3 / 6 (50.00%)
occurrences (all)	6	11	3
Hyperkalaemia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 28 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	7	0
Hypermagnesaemia			
subjects affected / exposed	1 / 12 (8.33%)	5 / 28 (17.86%)	1 / 6 (16.67%)
occurrences (all)	1	5	1
Hypernatraemia			
subjects affected / exposed	1 / 12 (8.33%)	3 / 28 (10.71%)	0 / 6 (0.00%)
occurrences (all)	3	3	0
Decreased appetite			
subjects affected / exposed	4 / 12 (33.33%)	13 / 28 (46.43%)	0 / 6 (0.00%)
occurrences (all)	4	14	0
Vitamin D deficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	3 / 12 (25.00%)	8 / 28 (28.57%)	2 / 6 (33.33%)
occurrences (all)	4	12	2
Hyponatraemia			
subjects affected / exposed	6 / 12 (50.00%)	13 / 28 (46.43%)	4 / 6 (66.67%)
occurrences (all)	8	15	4
Hypomagnesaemia			

subjects affected / exposed	2 / 12 (16.67%)	5 / 28 (17.86%)	0 / 6 (0.00%)
occurrences (all)	3	6	0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 28 (3.57%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Hypoglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 28 (7.14%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
Hypochloraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	4 / 12 (33.33%)	9 / 28 (32.14%)	2 / 6 (33.33%)
occurrences (all)	4	12	2
Hypoalbuminaemia			
subjects affected / exposed	6 / 12 (50.00%)	11 / 28 (39.29%)	2 / 6 (33.33%)
occurrences (all)	7	14	2
Hyperuricaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 28 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	3 / 12 (25.00%)	9 / 28 (32.14%)	3 / 6 (50.00%)
occurrences (all)	3	13	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2015	Clarified the correlative sample processing instructions and Endocrine and Autoimmune observations have been modified and the total required blood volumes have been significantly reduced.
30 October 2015	Added guidelines for management of pleural effusion as well as to add an additional cohort to Part B for enrollment of patients with relapsed or refractory neuroblastoma who are evaluable only for MIBG response. Also, a non-statistical cohort for melanoma patients was added.
07 July 2016	Added Part D. Additionally, the eligibility criteria have been modified to permit enrollment of patients with lymphoma who have previously received an allogeneic stem cell transplant.
17 January 2017	Updated the versions of the Comprehensive Adverse Events and Potential Risks (CAEPR) list.
24 February 2017	Stopping rules were added for the incidence of GVHD in lymphoma patients who enrolled following allogeneic stem cell transplant. Also, assessment of cardiac function, was added given the occurrence of myocarditis in patients using combination Ipi/Nivo in other studies.
09 August 2018	The revised toxicity profile (CAEPR) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised accordingly. This amendment also reflected the conversion of the protocol to CTCAE version 5.0.
02 April 2019	Added a new arm (Part E) to explore a different combination of nivolumab and ipilimumab in patients with rhabdomyosarcoma or Ewing Sarcoma/Peripheral PNET.
23 May 2019	Revised CAEPR for ipilimumab has been inserted in the protocol, and the associated risk information in the informed consent documents has been revised accordingly.
31 July 2019	This protocol has been amended to update the infusion time of nivolumab from 60 min to 30 min. Ipilimumab was infused over 90 min.
20 February 2020	Nivolumab drug information has been updated also included the addition of preclinical biomarker study information.
30 March 2020	Included the addition of off-study criteria for Part E patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported