



Clinical trial results:

A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination with Nivolumab in Advanced /Metastatic Solid Tumors and B Cell Non-Hodgkins Lymphoma

Summary

EudraCT number	2014-002241-22
Trial protocol	ES DE
Global end of trial date	24 May 2019

Results information

Result version number	v1 (current)
This version publication date	26 June 2020
First version publication date	26 June 2020

Trial information

Trial identification

Sponsor protocol code	CA186-107
-----------------------	-----------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb International Corporation, EU Study Start-Up Unit, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to determine the Safety and tolerability of Urelumab Administered in Combination with Nivolumab in Advanced /Metastatic Solid Tumors and B Cell Non-Hodgkins Lymphoma

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 subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United States: 154
Worldwide total number of subjects	228
EEA total number of subjects	74

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	118
From 65 to 84 years	107

85 years and over	3
-------------------	---

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

228 Participants were enrolled, 160 entered the treatment period, 68 did not entered , reasons for not entering the treatment period:7 withdrew consent, 54 did not meet study crieteria,1 adverse event, 2 death, 1 sponsor reason,2 other, 1 lost follow up.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TRT A

Arm description:

URE3 Q4WK+NIV3 Q2WK

Arm type	Experimental
Investigational medicinal product name	Urelumab
Investigational medicinal product code	BMS-663513
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

5mg/ml

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-936558
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

10mg/ml

Arm title	TRT B
------------------	-------

Arm description:

URE8 Q4WK+NIV3 Q2WK

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-936558
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

10mg/ml

Investigational medicinal product name	Urelumab
Investigational medicinal product code	BMS-663513
Other name	
Pharmaceutical forms	Injection

Routes of administration	Intravenous use
--------------------------	-----------------

Dosage and administration details:

5mg/ml

Arm title	TRT D
------------------	-------

Arm description:

URE8 Q4WK+NIV240mg Q2WK

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Urelumab
--	----------

Investigational medicinal product code	BMS-663513
--	------------

Other name	
------------	--

Pharmaceutical forms	Injection
----------------------	-----------

Routes of administration	Intravenous use
--------------------------	-----------------

Dosage and administration details:

5mg/ml

Investigational medicinal product name	Nivolumab
--	-----------

Investigational medicinal product code	BMS-936558
--	------------

Other name	
------------	--

Pharmaceutical forms	Injection
----------------------	-----------

Routes of administration	Intravenous use
--------------------------	-----------------

Dosage and administration details:

10mg/ml

Number of subjects in period 1^[1]	TRT A	TRT B	TRT D
Started	6	4	150
Completed	0	0	6
Not completed	6	4	144
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	-	-	3
Disease progression	4	3	98
Study drug toxicity	1	-	10
Adverse event, non-fatal	-	-	8
Unspecified	-	-	1
Subject discontinued study drug	1	-	1
Completed treatment as per protocol	-	1	22

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 228 Participants were enrolled, 160 entered the treatment period.

Baseline characteristics

Reporting groups

Reporting group title	TRT A
Reporting group description: URE3 Q4WK+NIV3 Q2WK	
Reporting group title	TRT B
Reporting group description: URE8 Q4WK+NIV3 Q2WK	
Reporting group title	TRT D
Reporting group description: URE8 Q4WK+NIV240mg Q2WK	

Reporting group values	TRT A	TRT B	TRT D
Number of subjects	6	4	150
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	1	2	67
>=65 years	5	2	83
Age Continuous Units: Years			
arithmetic mean	64.7	64.0	63.8
standard deviation	± 9.40	± 8.52	± 11.71
Sex: Female, Male Units: Participants			
Female	2	2	47
Male	4	2	103
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	9
White	6	4	136
More than one race	0	0	0
Unknown or Not Reported	0	0	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	5	2	107
Unknown or Not Reported	1	1	42

Reporting group values	Total		
Number of subjects	160		
Age Categorical Units: Participants			
<=18 years	0		

Between 18 and 65 years	70		
>=65 years	90		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	51		
Male	109		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	9		
White	146		
More than one race	0		
Unknown or Not Reported	4		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	114		
Unknown or Not Reported	44		

End points

End points reporting groups

Reporting group title	TRT A
Reporting group description: URE3 Q4WK+NIV3 Q2WK	
Reporting group title	TRT B
Reporting group description: URE8 Q4WK+NIV3 Q2WK	
Reporting group title	TRT D
Reporting group description: URE8 Q4WK+NIV240mg Q2WK	
Subject analysis set title	TRT D - NSCLC pd1/pd-l1 experienced
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE8 Q4WK+NIV240mg Q2WK- Non small cell lung cancer pd1/pd-l1 experienced	
Subject analysis set title	TRT D - NSCLC pd1/pd-l1 naive
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE8 Q4WK+NIV240mg Q2WK - Non small cell lung cancer pd1/pd-l1 naive.	
Subject analysis set title	TRT D - Melanoma pd1/pd-l1 experienced
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE8 Q4WK+NIV240mg Q2WK - Melanoma pd1/pd-l1 experienced	
Subject analysis set title	TRT A - Melanoma pd1/pd-l1 naive
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE3 Q4WK+NIV3 Q2WK - Melanoma pd1/pd-l1 naive	
Subject analysis set title	TRT B -
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE8 Q4WK+NIV3 Q2WK - Melanoma pd1/pd-l1 naive	
Subject analysis set title	TRT D - Melanoma pd1/pd-l1 naive
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE8 Q4WK+NIV240mg Q2WK - Melanoma pd1/pd-l1 naive	
Subject analysis set title	TRT A - SCCHN
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE3 Q4WK+NIV3 Q2WK - Squamous cell carcinoma of head and neck.	
Subject analysis set title	TRT D - SCCHN
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE8 Q4WK+NIV240mg Q2WK - Squamous cell carcinoma of head and neck.	
Subject analysis set title	TRT A - Other Solid Tumors
Subject analysis set type	Sub-group analysis
Subject analysis set description: URE3 Q4WK+NIV3 Q2WK - Other solid tumors	
Subject analysis set title	TRT B - Other Solid Tumors
Subject analysis set type	Sub-group analysis

Subject analysis set description:

URE8 Q4WK+NIV3 Q2WK - Other Solid tumors.

Subject analysis set title	TRT D - DLBCL
Subject analysis set type	Sub-group analysis

Subject analysis set description:

URE8 Q4WK+NIV240mg Q2WK - Diffuse Large B-cell lymphoma.

Subject analysis set title	TRT D - FL
Subject analysis set type	Sub-group analysis

Subject analysis set description:

URE8 Q4WK+NIV240mg Q2WK - Follicular Lymphoma.

Subject analysis set title	Urelumab ADA
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Urelumab Anti drug antibody

Subject analysis set title	Nivolumab ADA
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Nivolumab anti drug antibody

Primary: The incidence of Adverse events.

End point title	The incidence of Adverse events. ^[1]
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

From day 1 until 100 days after participant last dose of study drug.

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 were planned for this endpoint.

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	150	
Units: Number of participants	6	4	150	

Statistical analyses

No statistical analyses for this end point

Primary: The Incidence of serious adverse events.

End point title	The Incidence of serious adverse events. ^[2]
-----------------	---

End point description:

End point type	Primary
----------------	---------

End point timeframe:

From day 1 until 100 days after participant last dose of the study drug.

Notes:

[2] - 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 were planned for this endpoint.

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	150	
Units: Number of participants	3	3	86	

Statistical analyses

No statistical analyses for this end point

Primary: The incidence of death.

End point title	The incidence of death. ^[3]
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

From day 1 until 100 days after participant last dose of study drug.

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 were planned for this endpoint.

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	150	
Units: Number of participants	6	2	93	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (BOR)

End point title	Best Overall Response (BOR)
-----------------	-----------------------------

End point description:

The total number of subjects whose best overall response (BOR) is either a complete response or partial response for solid tumors and complete remission or partial remission for B-cell NHL, divided by the total number of subjects in the population of interest.

End point type	Secondary
----------------	-----------

End point timeframe:

Every 8 weeks for Cycle 1 through Cycle 6 then every 12 weeks thereafter for approximately 2 years.

End point values	TRT D - NSCLC pd1/pd-l1 experienced	TRT D - NSCLC pd1/pd-l1 naïve	TRT D - Melanoma pd1/pd-l1 experienced	TRT A - Melanoma pd1/pd-l1 naïve
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	20	4
Units: Number of participants				
Complete response	0	0	0	0
Partial response	1	1	2	1

End point values	TRT B -	TRT D - Melanoma pd1/pd-l1 naïve	TRT A - SCCHN	TRT D - SCCHN
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	43	1	21
Units: Number of participants				
Complete response	1	6	0	1
Partial response	0	15	0	0

End point values	TRT A - Other Solid Tumors	TRT B - Other Solid Tumors	TRT D - DLBCL	TRT D - FL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	22	4
Units: Number of participants				
Complete response	0	0	0	0
Partial response	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)
-----------------	-------------------------------

End point description:

Objective response rate (ORR) is defined as the total number of subjects whose BOR is either CR or PR divided by the total number of subjects in the population of interest.

End point type	Secondary
----------------	-----------

End point timeframe:

Every 8 weeks for Cycle 1 through Cycle 6 then every 12 weeks thereafter for approximately 2 years.

End point values	TRT D - NSCLC pd1/pd-l1 experienced	TRT D - NSCLC pd1/pd-l1 naïve	TRT D - Melanoma pd1/pd-l1 experienced	TRT A - Melanoma pd1/pd-l1 naïve
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	20	20	4
Units: Percentage of participants				
number (confidence interval 95%)	5.0 (0.1 to 24.9)	5.0 (0.1 to 24.9)	10.0 (1.2 to 31.7)	25.0 (0.6 to 80.6)

End point values	TRT B -	TRT D - Melanoma pd1/pd-l1 naïve	TRT A - SCCHN	TRT D - SCCHN
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	43	1	21
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (2.5 to 100.0)	48.8 (33.3 to 64.5)	0 (0.0 to 97.5)	4.8 (0.1 to 23.8)

End point values	TRT A - Other Solid Tumors	TRT B - Other Solid Tumors	TRT D - DLBCL	TRT D - FL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	3	22	4
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 97.5)	0 (0.0 to 70.8)	0 (0.0 to 16.1)	0 (0.0 to 60.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)
End point description:	
DOR is defined as the number of days between the date of first response and the subsequent date of objectively documented disease progression based on the criteria (RECIST v1.1) or relapse based on IWG, or death due to any cause, if death occurred within 100 days after last dose, whichever occurs first. Data was not collected due to discontinuation of the study/Due to study termination.	
End point type	Secondary
End point timeframe:	
Every 8 weeks for Cycle 1 through Cycle 6 then every 12 weeks thereafter for approximately 2 years	

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[4]	4 ^[5]	150 ^[6]	
Units: Months	9999	9999	9999	

Notes:

[4] - Data was not collected due to discontinuation of the study/Due to study termination

[5] - Data was not collected due to discontinuation of the study/Due to study termination

[6] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival rate (PFSR)

End point title	Progression-free survival rate (PFSR)
-----------------	---------------------------------------

End point description:

PFSR is defined as the probability of a subject remaining progression-free and surviving a specific length of time. Data was not collected due to discontinuation of the study/Due to study termination.

End point type	Secondary
----------------	-----------

End point timeframe:

Every 8 weeks for Cycle 1 through Cycle 6 then every 12 weeks thereafter for approximately 2 years.

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[7]	4 ^[8]	150 ^[9]	
Units: Number of participants	9999	9999	9999	

Notes:

[7] - Data was not collected due to discontinuation of the study/Due to study termination

[8] - Data was not collected due to discontinuation of the study/Due to study termination

[9] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed serum concentration (Cmax)

End point title	Maximum observed serum concentration (Cmax)
-----------------	---

End point description:

Data was not collected due to discontinuation of the study/Due to study termination.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycles 1, 2, 3, 4, 6, and followup Days up to 100 days.

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[10]	4 ^[11]	150 ^[12]	
Units: µg/mL	9999	9999	9999	

Notes:

[10] - Data was not collected due to discontinuation of the study/Due to study termination

[11] - Data was not collected due to discontinuation of the study/Due to study termination

[12] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Time of maximum observed serum concentration (Tmax)

End point title	Time of maximum observed serum concentration (Tmax)
End point description: Data was not collected due to discontinuation of the study/Due to study termination.	
End point type	Secondary
End point timeframe: Cycles 1, 2, 3, 4, 6, and followup Days up to 100 days.	

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[13]	4 ^[14]	150 ^[15]	
Units: Hours	9999	9999	9999	

Notes:

[13] - Data was not collected due to discontinuation of the study/Due to study termination

[14] - Data was not collected due to discontinuation of the study/Due to study termination

[15] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve in one dosing interval (AUCTAU)

End point title	Area under the concentration-time curve in one dosing interval (AUCTAU)
End point description: Data was not collected due to discontinuation of the study/Due to study termination.	
End point type	Secondary
End point timeframe: Cycles 1, 2, 3, 4, 6, and followup Days up to 100 days	

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[16]	4 ^[17]	150 ^[18]	
Units: µg.hr/mL	9999	9999	9999	

Notes:

[16] - Data was not collected due to discontinuation of the study/Due to study termination

[17] - Data was not collected due to discontinuation of the study/Due to study termination

[18] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Trough observed plasma concentration(Ctrough)

End point title	Trough observed plasma concentration(Ctrough)
End point description: Data was not collected due to discontinuation of the study/Due to study termination.	
End point type	Secondary
End point timeframe: Cycles 1, 2, 3, 4, 6, and followup Days up to 100 days.	

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[19]	4 ^[20]	150 ^[21]	
Units: µg/mL	9999	9999	9999	

Notes:

[19] - Data was not collected due to discontinuation of the study/Due to study termination

[20] - Data was not collected due to discontinuation of the study/Due to study termination

[21] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: End of infusion concentration (Ceoinf)

End point title	End of infusion concentration (Ceoinf)
End point description: Data was not collected due to discontinuation of the study/Due to study termination.	
End point type	Secondary
End point timeframe: Cycles 1, 2, 3, 4, 6, and followup Days up to 100 days.	

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[22]	4 ^[23]	150 ^[24]	
Units: Number	9999	9999	9999	

Notes:

[22] - Data was not collected due to discontinuation of the study/Due to study termination

[23] - Data was not collected due to discontinuation of the study/Due to study termination

[24] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve, 0 to time of last quantifiable concentration (AUC(0-T))

End point title	Area under the plasma concentration-time curve, 0 to time of last quantifiable concentration (AUC(0-T))
-----------------	---

End point description:

Data was not collected due to discontinuation of the study/Due to study termination.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycles 1, 2, 3, 4, 6, and followup Days up to 100 days.

End point values	TRT A	TRT B	TRT D	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[25]	4 ^[26]	150 ^[27]	
Units: µg.hr/mL	9999	9999	9999	

Notes:

[25] - Data was not collected due to discontinuation of the study/Due to study termination

[26] - Data was not collected due to discontinuation of the study/Due to study termination

[27] - Data was not collected due to discontinuation of the study/Due to study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of specific anti-drug antibodies (ADA) to Urelumab and Nivolumab

End point title	Occurrence of specific anti-drug antibodies (ADA) to Urelumab and Nivolumab
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Cycles 1, 2, 3, 4, 6, and followup Days up to 100 days.

End point values	Urelumab ADA	Nivolumab ADA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	133	128		
Units: Number of participants				
Baseline ADA positive	5	2		
ADA positive	55	9		
ADA negative	78	119		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from start of treatment up to 30 days after last dose of study treatment.

Adverse event reporting additional description:

Analysis was performed in All treated subjects defined as all subjects who received at least one dose of any study medication.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	TRT A: URE3 Q4WK+NIV3 Q2WK
-----------------------	----------------------------

Reporting group description:

Subjects were intravenously (IV) administered with 3 milligrams per kilogram of body weight (mg/kg) of Urelumab, once every 4 weeks (Q4WK) along with Nivolumab 3 mg/kg IV, every 2 weeks (Q2WK).

Reporting group title	TRT B: URE8 Q4WK+NIV3 Q2WK
-----------------------	----------------------------

Reporting group description:

Subjects were IV administered with 8 mg/kg of Urelumab, Q4WK along with Nivolumab 3 mg/kg IV, Q2WK.

Reporting group title	TRT D: URE8 Q4WK+NIV240mg Q2WK
-----------------------	--------------------------------

Reporting group description:

Subjects were IV administered with 8 mg/kg of Urelumab, Q4WK along with Nivolumab 240 mg IV, Q2WK.

Serious adverse events	TRT A: URE3 Q4WK+NIV3 Q2WK	TRT B: URE8 Q4WK+NIV3 Q2WK	TRT D: URE8 Q4WK+NIV240mg Q2WK
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	3 / 4 (75.00%)	90 / 150 (60.00%)
number of deaths (all causes)	1	1	50
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	45 / 150 (30.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 48
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 42
Metastases to central nervous system			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthermia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothermia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
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			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	4 / 150 (2.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic mass			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	5 / 150 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrothorax			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pleural effusion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	4 / 150 (2.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia aspiration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Persistent depressive disorder			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-Glutamyltransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central nervous system lesion			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haematoma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Monoplegia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (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
Faecaloma			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (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 tract obstruction			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypogonadism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
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 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations Bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 2 0 / 0
Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 1 0 / 0
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 1 0 / 0
Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 1 0 / 0
Erysipelas subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 2 0 / 0
Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	7 / 150 (4.67%) 0 / 8 0 / 1
Pneumonia haemophilus subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 2 0 / 0
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 6 (0.00%) 0 / 0 0 / 0	0 / 4 (0.00%) 0 / 0 0 / 0	1 / 150 (0.67%) 0 / 1 0 / 0
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	TRT A: URE3 Q4WK+NIV3 Q2WK	TRT B: URE8 Q4WK+NIV3 Q2WK	TRT D: URE8 Q4WK+NIV240mg Q2WK
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 6 (100.00%)	4 / 4 (100.00%)	147 / 150 (98.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Basal cell carcinoma subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	1 / 150 (0.67%) 1
Squamous cell carcinoma subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	1 / 150 (0.67%) 1
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	1 / 150 (0.67%) 1
Hypertension subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 4 (0.00%) 0	4 / 150 (2.67%) 4
Hypotension subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	0 / 4 (0.00%) 0	7 / 150 (4.67%) 8
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 4 (25.00%) 1	16 / 150 (10.67%) 17
Chills subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0	14 / 150 (9.33%) 14
Fatigue subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 5	2 / 4 (50.00%) 2	62 / 150 (41.33%) 73
Gait disturbance subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	1 / 150 (0.67%) 1
Oedema peripheral			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	26 / 150 (17.33%) 31
Performance status decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	1 / 150 (0.67%) 1
Pyrexia subjects affected / exposed occurrences (all)	4 / 6 (66.67%) 4	1 / 4 (25.00%) 1	30 / 150 (20.00%) 40
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 4 (0.00%) 0	34 / 150 (22.67%) 37
Dyspnoea subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 4 (0.00%) 0	26 / 150 (17.33%) 32
Nasal congestion subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	6 / 150 (4.00%) 6
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	1 / 150 (0.67%) 1
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0	11 / 150 (7.33%) 12
Depression subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	3 / 150 (2.00%) 3
Insomnia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0	11 / 150 (7.33%) 11
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 3	0 / 4 (0.00%) 0	26 / 150 (17.33%) 40
Amylase increased			

subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	14 / 150 (9.33%)
occurrences (all)	0	0	16
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	26 / 150 (17.33%)
occurrences (all)	0	1	39
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	20 / 150 (13.33%)
occurrences (all)	2	1	25
Blood creatinine increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	10 / 150 (6.67%)
occurrences (all)	2	0	12
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	5 / 150 (3.33%)
occurrences (all)	0	3	6
Blood uric acid decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1
Lipase increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	18 / 150 (12.00%)
occurrences (all)	2	0	30
Lymphocyte count decreased			
subjects affected / exposed	2 / 6 (33.33%)	0 / 4 (0.00%)	12 / 150 (8.00%)
occurrences (all)	3	0	15
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	11 / 150 (7.33%)
occurrences (all)	1	0	17
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	13 / 150 (8.67%)
occurrences (all)	2	0	17
Weight decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	18 / 150 (12.00%)
occurrences (all)	1	0	18
Gamma-Glutamyltransferase increased			

subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	1 / 4 (25.00%) 1	18 / 150 (12.00%) 22
Thyroxine free decreased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	0 / 150 (0.00%) 0
Tri-Iodothyronine decreased subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0	1 / 150 (0.67%) 1
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0	8 / 150 (5.33%) 13
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2	1 / 4 (25.00%) 1	9 / 150 (6.00%) 11
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 2	2 / 150 (1.33%) 3
Skin abrasion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	1 / 150 (0.67%) 1
Sunburn subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	1 / 150 (0.67%) 2
Nervous system disorders			
Balance disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	1 / 150 (0.67%) 1
Carotid artery occlusion subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	0 / 150 (0.00%) 0
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1	1 / 150 (0.67%) 1
Dizziness			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	13 / 150 (8.67%)
occurrences (all)	1	0	17
Headache			
subjects affected / exposed	4 / 6 (66.67%)	0 / 4 (0.00%)	23 / 150 (15.33%)
occurrences (all)	5	0	28
Peripheral motor neuropathy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences (all)	2	0	3
Restless legs syndrome			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 150 (0.67%)
occurrences (all)	0	1	1
Sciatica			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 150 (0.00%)
occurrences (all)	0	1	0
Sinus headache			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1
Dysgeusia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences (all)	1	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 6 (50.00%)	2 / 4 (50.00%)	51 / 150 (34.00%)
occurrences (all)	6	2	63
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	5 / 150 (3.33%)
occurrences (all)	0	1	5
Lacrimation increased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	2 / 150 (1.33%)
occurrences (all)	0	1	2
Vision blurred			

subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2	0 / 4 (0.00%) 0	2 / 150 (1.33%) 3
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 150 (0.00%)
occurrences (all)	0	1	0
Abdominal distension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	6 / 150 (4.00%)
occurrences (all)	1	0	6
Abdominal pain			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	19 / 150 (12.67%)
occurrences (all)	2	1	20
Abdominal pain upper			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	6 / 150 (4.00%)
occurrences (all)	1	0	7
Anal incontinence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1
Ascites			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 150 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	33 / 150 (22.00%)
occurrences (all)	1	0	37
Dental caries			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 150 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	5 / 6 (83.33%)	0 / 4 (0.00%)	32 / 150 (21.33%)
occurrences (all)	9	0	45
Dry mouth			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	8 / 150 (5.33%)
occurrences (all)	1	0	8
Dysphagia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	6 / 150 (4.00%)
occurrences (all)	2	1	6

Gastritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	3 / 150 (2.00%)
occurrences (all)	0	1	3
Lip swelling			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 150 (0.00%)
occurrences (all)	0	1	0
Melaena			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	3 / 6 (50.00%)	0 / 4 (0.00%)	37 / 150 (24.67%)
occurrences (all)	4	0	49
Vomiting			
subjects affected / exposed	3 / 6 (50.00%)	0 / 4 (0.00%)	27 / 150 (18.00%)
occurrences (all)	4	0	37
Hepatobiliary disorders			
Hepatic haemorrhage			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 6 (16.67%)	1 / 4 (25.00%)	5 / 150 (3.33%)
occurrences (all)	1	3	5
Drug eruption			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences (all)	1	0	3
Dry skin			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	13 / 150 (8.67%)
occurrences (all)	0	0	13
Hyperkeratosis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences (all)	1	0	0
Lichen planus			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	2 / 4 (50.00%)	22 / 150 (14.67%)
occurrences (all)	0	2	25
Rash			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	17 / 150 (11.33%)
occurrences (all)	0	2	24
Rash macular			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences (all)	1	0	2
Rash maculo-papular			
subjects affected / exposed	0 / 6 (0.00%)	2 / 4 (50.00%)	9 / 150 (6.00%)
occurrences (all)	0	3	11
Rash papular			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	0 / 150 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences (all)	1	0	3
Skin ulcer			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	3 / 150 (2.00%)
occurrences (all)	1	0	3
Pollakiuria			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	6 / 150 (4.00%)
occurrences (all)	1	0	6
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences (all)	1	0	2
Hypothyroidism			

subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	17 / 150 (11.33%)
occurrences (all)	0	1	17
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 4 (50.00%)	18 / 150 (12.00%)
occurrences (all)	0	4	27
Back pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	24 / 150 (16.00%)
occurrences (all)	0	0	25
Flank pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	1 / 150 (0.67%)
occurrences (all)	0	1	1
Muscular weakness			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	5 / 150 (3.33%)
occurrences (all)	3	1	6
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	11 / 150 (7.33%)
occurrences (all)	0	0	11
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	15 / 150 (10.00%)
occurrences (all)	0	1	16
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	6 / 150 (4.00%)
occurrences (all)	0	1	6
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	15 / 150 (10.00%)
occurrences (all)	0	0	17
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences (all)	1	0	0
Gingivitis			

subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1
Localised infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	0 / 150 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	6 / 150 (4.00%)
occurrences (all)	0	1	8
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	4 / 150 (2.67%)
occurrences (all)	1	0	4
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	12 / 150 (8.00%)
occurrences (all)	1	0	14
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	12 / 150 (8.00%)
occurrences (all)	1	0	16
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 6 (33.33%)	1 / 4 (25.00%)	24 / 150 (16.00%)
occurrences (all)	3	1	26
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	4 / 150 (2.67%)
occurrences (all)	1	0	6
Hypercalcaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	8 / 150 (5.33%)
occurrences (all)	0	0	8
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	15 / 150 (10.00%)
occurrences (all)	0	0	22
Hyperkalaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	11 / 150 (7.33%)
occurrences (all)	3	0	23
Hypermagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	1 / 150 (0.67%)
occurrences (all)	1	0	1

Hyperuricaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	2 / 150 (1.33%)
occurrences (all)	2	0	3
Hypoalbuminaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	12 / 150 (8.00%)
occurrences (all)	0	0	13
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 4 (25.00%)	9 / 150 (6.00%)
occurrences (all)	0	1	11
Hypomagnesaemia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 4 (0.00%)	6 / 150 (4.00%)
occurrences (all)	1	0	6
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 4 (0.00%)	14 / 150 (9.33%)
occurrences (all)	0	0	18
Hypophosphataemia			
subjects affected / exposed	3 / 6 (50.00%)	0 / 4 (0.00%)	16 / 150 (10.67%)
occurrences (all)	3	0	23

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2015	To implement changes to inclusion/exclusion criteria, clarify requirements and assessments for treatment beyond disease progression and criteria for allowing treatment to resume after a dose delay due to toxicity, add time and events schedules for subjects eligible for retreatment, and clarify PK sampling and biomarker assessments.
29 June 2015	To implement a change in duration to combination therapy and use of flat dosing for subjects enrolled following approval of Revised Protocol 02
30 August 2015	Discontinue enrollment into Cohorts A, B, C, D. Implement an update to exclusion Criteria.
22 December 2015	To expand the study population for cohort expansion to include subjects with follicular lymphoma and to further differentiate subjects with non-small-cell lung cancer into two separate groups (those with no prior anti PD-1/anti-PD-L1 therapy and those who have relapsed or are refractory to prior anti-PD-1/anti-PD-L1).
09 May 2016	To clarify application to new cohort of subjects with NSCLC and melanoma who have relapsed or are refractory to prior anti-PD-1/anti-PD-L1 therapy and exception for NSCLC and MEL subjects enrolling in the expansion cohorts where prior anti-PD-1 or anti-PD-L1 therapies are specifically required. To include a cohort of NSCLC and melanoma subjects who have relapsed or are refractory to prior anti-PD-1/anti-PD-L1 therapy.
22 March 2017	In order to further explore an emerging efficacy signal, additional patients with previously untreated metastatic melanoma (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma) subjects with PD-L1 negative tumors (<1%) will be enrolled under this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported