Clinical trial results:
Phase 1b/Phase 3 Multicenter Study of Avelumab (MSB0010718C) in Combination Regimens That Include an Immune Agonist, Epigenetic Modulator, CD20 Antagonist and/or Conventional Chemotherapy in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

Summary

EudraCT number	2016-002904-15
Trial protocol	BE DE SE CZ GB ES DK FR
Global end of trial date	02 December 2019

Results information

Result version number	v1 (current)
This version publication date	05 December 2020
First version publication date	05 December 2020

Trial information

Trial identification

Sponsor protocol code	B9991011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02951156
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	06 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To asses safety, efficacy, and potentially select the most active treatment regimen among 3 treatment arms to advance to the Phase 3 component of the study.

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 Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	29
EEA total number of subjects	7

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)	10
From 65 to 84 years	17
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study included subjects with relapsed or refractory DLBCL after completion of at least 2 and not more than 4 lines of rituximab-containing multi-agent chemotherapy (prior to this study), and/or in whom autologous stem cell transplant (ASCT) has failed, or who were not candidates for ASCT or who were not eligible for intensive chemotherapy.

Pre-assignment

Screening details:

A total of 41 subjects were screened and 29 subjects were randomised in the study.

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	Avelumab+Rituximab+Utomilumab

Arm description:

Avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 milligram per meter square (mg/m^2) IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab was well tolerated, then it was administered on Day 1 of Cycle 3 and all subsequent cycles until the subject no longer received clinical benefit. The duration of each treatment cycle was 28 days.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab 10 mg/kg IV infusion was administered on Day 2 and Day 16 of Cycles 1 and 2/Day 1 and Day 15 in Cycle 3 and all subsequent cycles.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375 mg/m^2 IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles).

Investigational medicinal product name	Utomilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Fixed dose of utomilumab 100 mg IV infusion on Day 2 of Cycles 1 and 2/Day 1 of Cycle 3 and all subsequent cycles.

Arm title	Avelumab+Azacitidine+Utomilumab

Arm description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Azacitidine 40 mg/m^2 subcutaneous (SC) dose was administered on Days 1 to 5 of each treatment cycle until the subject no longer received clinical benefit, along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab was well tolerated, then it was administered on Day 1 of Cycle 3 and all subsequent cycles until the subject no longer received clinical benefit. The duration of each treatment cycle was 28 days.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab 10 mg/kg IV infusion was administered on Day 2 and Day 16 of Cycles 1 and 2/Day 1 and Day 15 in Cycle 3 and all subsequent cycles.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Azacitidine 40 mg/m^2 SC dose was administered on Days 1 to 5 of each treatment cycle.

Investigational medicinal product name	Utomilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Fixed dose of utomilumab 100 mg IV infusion on Day 2 of Cycles 1 and 2/Day 1 of Cycle 3 and all subsequent cycles.

Arm title	Avelumab+Bendamustine+Rituximab

Arm description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 mg/m^2 IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with 90 mg/m^2 IV infusion of bendamustine on Day 2 and Day 3 of each treatment cycle in Cycles 1 and 2. If the dose of bendamustine was well tolerated, then it was administered on Day 1 and Day 2 in Cycle 3 and all subsequent cycles for a maximum of 6 cycles. The duration of each treatment cycle was 28 days.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Avelumab 10 mg/kg IV infusion was administered on Day 2 and Day 16 of Cycles 1 and 2/Day 1 and Day 15 in Cycle 3 and all subsequent cycles.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375 mg/m^2 IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles).

Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine 90 mg/m^2 infusion was administered on Day 2 and Day 3 of each treatment cycle in Cycles 1 and 2/Day 1 and Day 2 in Cycle 3 and all subsequent cycles (maximum of 6 cycles).

Number of subjects in period 1	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab
Started	9	9	11
Completed	0	0	1
Not completed	9	9	10
Consent withdrawn by subject	-	-	1
Death	3	8	5
Study terminated by sponsor	-	-	1
Unspecified	5	1	2
Progressive disease	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab+Rituximab+Utomilumab

Reporting group description:

Avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 milligram per meter square (mg/m^2) IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab was well tolerated, then it was administered on Day 1 of Cycle 3 and all subsequent cycles until the subject no longer received clinical benefit. The duration of each treatment cycle was 28 days.

Reporting group title	Avelumab+Azacitidine+Utomilumab

Reporting group description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Azacitidine 40 mg/m^2 subcutaneous (SC) dose was administered on Days 1 to 5 of each treatment cycle until the subject no longer received clinical benefit, along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab was well tolerated, then it was administered on Day 1 of Cycle 3 and all subsequent cycles until the subject no longer received clinical benefit. The duration of each treatment cycle was 28 days.

Reporting group title	Avelumab+Bendamustine+Rituximab

Reporting group description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 mg/m^2 IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with 90 mg/m^2 IV infusion of bendamustine on Day 2 and Day 3 of each treatment cycle in Cycles 1 and 2. If the dose of bendamustine was well tolerated, then it was administered on Day 1 and Day 2 in Cycle 3 and all subsequent cycles for a maximum of 6 cycles. The duration of each treatment cycle was 28 days.

Reporting group values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab
Number of subjects	9	9	11
Age Categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	2	3	5
>=65 years	7	6	6
Age continuous Units: years			
arithmetic mean	69.00	66.67	66.64
standard deviation	± 5.79	± 13.11	± 15.16
Sex: Female, Male Units:			
Female	0	3	2
Male	9	6	9
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	0	0	0
White	8	8	11
More than one race	0	0	0
Other	1	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	7	8	11
Unknown or Not Reported	2	0	0

Reporting group values	Total		
Number of subjects	29		
Age Categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	10		
>=65 years	19		
Age continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units:			
Female	5		
Male	24		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	27		
More than one race	0		
Other	2		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	26		
Unknown or Not Reported	2		

End points

End points reporting groups

Reporting group title	Avelumab+Rituximab+Utomilumab

Reporting group description:

Avelumab 10 milligram per kilogram (mg/kg) intravenous (IV) infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 milligram per meter square (mg/m^2) IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab was well tolerated, then it was administered on Day 1 of Cycle 3 and all subsequent cycles until the subject no longer received clinical benefit. The duration of each treatment cycle was 28 days.

Reporting group title	Avelumab+Azacitidine+Utomilumab

Reporting group description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Azacitidine 40 mg/m^2 subcutaneous (SC) dose was administered on Days 1 to 5 of each treatment cycle until the subject no longer received clinical benefit, along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab was well tolerated, then it was administered on Day 1 of Cycle 3 and all subsequent cycles until the subject no longer received clinical benefit. The duration of each treatment cycle was 28 days.

Reporting group title	Avelumab+Bendamustine+Rituximab

Reporting group description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycles 1 and 2, if well tolerated then continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 mg/m^2 IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with 90 mg/m^2 IV infusion of bendamustine on Day 2 and Day 3 of each treatment cycle in Cycles 1 and 2. If the dose of bendamustine was well tolerated, then it was administered on Day 1 and Day 2 in Cycle 3 and all subsequent cycles for a maximum of 6 cycles. The duration of each treatment cycle was 28 days.

Primary: Number of Subjects With Dose Limiting Toxicities (DLT)

End point title	Number of Subjects With Dose Limiting Toxicities (DLT)[1]

End point description:

AEs occurring in first 4 weeks of treatment,attributable to 1 of study drugs. Hematology:1)Grade (G) 4 neutropenia,2)G >=3 febrile neutropenia with single temperature of >38.3 degrees Celsius (C)/sustained temperature of >=38.0 degrees C for more than 1 hour with/without associated sepsis,3)G>=3 neutropenic infection,4) G 4 thrombocytopenia/G 3 thrombocytopenia with clinically significant bleeding,5)G 4 anemia 6)Any grade >=3 non-hematology toxicity except:transient G 3 flu like symptoms/fever controlled with standard medical management;transient G 3 fatigue,localized skin reactions/headache that resolves to Grade <=1;G 3 nausea,vomiting/diarrhea resolved to Grade <=1 in 72 hours after initiation of adequate medical management;Grade 3 skin toxicity resolved to G <=1 in 7 days;tumor flare;Single laboratory values that are out of normal range,that have noclinical correlate and resolve to Grade <=1 within 7 days with adequate medical management. DLT evaluable set analysed.

End point type	Primary

End point timeframe:

Day 1 Cycle 1 up to 4 Weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was analyzed only in the reporting arms identified

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	5	10	
Units: Subjects	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR) as Assessed by Investigator per Lugano Response Classification Criteria

End point title	Objective Response Rate (ORR) as Assessed by Investigator per Lugano Response Classification Criteria[2]

End point description:

Objective response rate (ORR) was defined as percentage of participants with complete response (CR) or partial response (PR), as assessed by investigator per lugano response classification criteria. CR was defined as a score of 1 (no uptake above background), 2 (uptake less than or equal to [<=] mediastinum), or 3 (uptake less than [<] mediastinum but <=liver) with or without a residual mass on PET 5-point scale (5-PS), for lymph nodes and extralymphatic sites; no new lesions; no evidence of fluorodeoxyglucose (FDG)-avid disease in bone marrow. PR was defined as >=50% decrease in SPD of up to six of the largest dominant lymph nodes, no increase in size of other nodes, liver, or spleen volume, a >=50% decrease in sum of products of diameters (SPD) of hepatic and splenic nodules, absence of other organ involvement, and no new sites of disease. Full analysis set (FAS) population analysed.

End point type	Primary

End point timeframe:

Randomization until date of PD, start of new anticancer therapy, discontinuation from study or death due to any cause, whichever occurred first (maximum up to 36 months)

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 descriptive data was planned to be reported for this endpoint

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	11	
Units: Percentage of subjects				
number (confidence interval 95%)	11.1 (0.3 to 48.2)	0 (0.0 to 33.6)	27.3 (6.0 to 61.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) Greater Than or Equal to (>=) Grade 3, As per National Cancer Institute Common Terminology Criteria For Adverse Events (NCI-CTCAE), Version 4.03

End point title	Number of Subjects With Treatment-Emergent Adverse Events

	(TEAEs) Greater Than or Equal to (>=) Grade 3, As per National Cancer Institute Common Terminology Criteria For Adverse Events (NCI-CTCAE), Version 4.03

End point description:

AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. As per NCI-CTCAE version 4.03,severity was graded as Grade(G)1: asymptomatic/mild symptoms, clinical/diagnostic observations only, intervention not indicated; G2:moderate, minimal, local/noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily life (ADL); G3: severe/medically significant but not immediately life-threatening, hospitalisation/prolongation of existing hospitalisation indicated, disabling, limiting self-care ADL; G4:life-threatening consequence, urgent intervention indicated; G5:death related to AE. TEAE was defined as events which occurred during on-treatment period beginning with first dose of study treatment through minimum (30 days + last dose of study treatment/start of new anti-cancer drug therapy). In this endpoint subject with any TEAE of G3 or above are reported. Safety analysis set (SAS)

End point type	Secondary

End point timeframe:

From first dose of study treatment up to at least 30 days after the last dose of study treatment or initiation of new anti-cancer therapy (up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	11	
Units: Subjects	4	7	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities As per National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point title	Number of Subjects With Laboratory Abnormalities As per National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 4.03

End point description:

Laboratory parameters included hematological and biochemistry: Hematological parameters included: anemia, haemoglobin increased, lymphocyte count decreased, lymphocyte count increased, neutrophil count decreased, platelet count decreased and white blood cells decreased. Biochemistry parameters included: alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, cholesterol high, cpk increased,creatinine increased, gamma glutamyl transferase(ggt)increased,hypercalcemia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia,hypertriglyceridemia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia,lipase increased, serum amylase increased. Abnormalities were graded by NCI CTCAE version 4.03 as G1=mild; G2=moderate; G3/G4=severe/life-threatening. SAS analysed. Here, n=subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

From first dose of study treatment up to at least 30 days after the last dose of study treatment or initiation of new anti-cancer therapy (up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	11	
Units: Subjects				
Anemia (n=8,8,10)	6	8	10	
Hemoglobin increased (n=8,8,10)	0	0	0	
Lymphocyte count decreased(n=7,8,10)	4	7	9	
Lymphocyte count increased(n=7,8,10)	0	0	0	
Neutrophil count decreased(n=8,8,10)	2	2	9	
Platelet count decreased(n=8,8,10)	4	3	8	
White blood cell decreased(n=7,8,10)	1	4	8	
Alanine aminotransferase increased (n=7,8,10)	2	5	2	
Alkaline phosphatase increased(n=7,8,10)	3	4	6	
Aspartate aminotransferase increased(n=7,8,9)	3	6	3	
Blood bilirubin increased(n=7,8,10)	0	3	3	
Cholesterol high(n=7,7,10)	2	3	3	
Cpk increased (n=7,7,10)	2	1	2	
Creatinine increased(n=7,8,10)	6	6	10	
GGT increased(n=7,7,10)	3	4	6	
Hypercalcemia(n=7,8,10)	0	3	2	
Hyperglycemia(n=7,8,10)	3	1	2	
Hyperkalemia(n=8,8,10)	0	0	2	
Hypermagnesemia(n=7,8,10)	1	1	1	
Hypernatremia (n=7,8,10)	0	0	1	
Hypertriglyceridemia (n=7,6,10)	3	3	7	
Hypoalbuminemia (n=7,8,10)	3	4	6	
Hypocalcemia (n=7,8,10)	1	0	2	
Hypoglycemia (n=7,8,10)	0	0	1	
Hypokalemia (n=8,8,10)	1	1	4	
Hypomagnesemia (n=7,8,10)	0	0	4	
Hyponatremia (n=7,8,10)	0	1	3	
Hypophosphatemia (n=7,7,10)	1	0	5	
Lipase increased (n=7,7,10)	1	2	3	
Serum amylase increased (n=7,7,10)	2	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Electrocardiogram (ECG) Abnormalities

End point title	Number of Subjects With Electrocardiogram (ECG) Abnormalities

End point description:

ECG abnormalities included: 1) QT interval, QT interval corrected using Bazett's formula (QTcB) and QT interval corrected using Fridericia's formula (QTcF): increase from baseline greater than (>) 30 millisecond (ms) or 60 ms; absolute value >450 ms, >480 ms and >500 ms; 2) heart rate (HR): absolute value <=50 beats per minute (bpm) and decrease from baseline >=20 bpm; absolute value >=120 bpm and increase from baseline >=20 bpm; 3) PR interval: absolute value >=220 ms and increase from baseline >=20 ms; 4) QRS interval: absolute value >=120 ms. Safety analysis set population included all subjects who received at least 1 dose of study drug. Here, n=subjects evaluable for specified rows.

End point type	Secondary

End point timeframe:

From first dose of study treatment up to at least 30 days after the last dose of study treatment or initiation of new anti-cancer therapy (up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	11	
Units: Subjects				
QT: IFB:>30 ms (n=8,9,11)	4	4	4	
QT: IFB: >60 ms (n=8,9,11)	1	3	2	
QT: >450 ms (n=8,9,11)	2	2	2	
QT: >480 ms (n= 8,9,11)	0	1	1	
QT: >500 ms (n=8,9,11)	0	0	0	
QTcB: IFB: >30 ms (n=7,9,10)	1	3	4	
QTcB: IFB: >60 ms (n=7,9,10)	1	1	0	
QTcB: >450 ms (n=7,9,11)	4	5	9	
QTcB: >480 ms (n=7,9,11)	2	3	4	
QTcB: >500 ms (n=7,9,11)	1	2	1	
QTcF: IFB: >30 ms (n=7,9,10)	1	3	3	
QTcF: IFB: >60 ms (n=7,9,10)	0	2	0	
QTcF: >450 ms (n=7,9,11)	4	3	6	
QTcF: >480 ms (n=7,9,11)	0	2	0	
QTcF: >500 ms (n=7,9,11)	0	2	0	
HR: <=50 bpm and DFB >=20bpm (n=7,9,10)	0	1	0	
HR: >=120 bpm and IFB >=20bpm (n=7,9,10)	0	0	1	
PR: >=220 ms and IFB >=20 ms (n=8,8,11)	0	0	0	
QRS: >=120 ms (n=8,9,11)	1	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as Assessed by Investigator per Lugano Response Classification Criteria

End point title	Duration of Response (DOR) as Assessed by Investigator per Lugano Response Classification Criteria

End point description:

DOR in subjects with OR as time from first documentation of OR to time of PD/death due to any cause, whichever occurred first. CR: score of 1(no uptake above background),2(uptake <=mediastinum),or 3(uptake <mediastinum but <=liver)with/without residual mass on PET 5-PS,for lymph nodes extralymphatic sites; no new lesions; no evidence of FDG-avid disease in bone marrow.PR:>=50% decrease in SPD of up to 6 of largest dominant lymph nodes, no increase in size of other nodes, liver, spleen volume,>=50% decrease in SPD of hepatic splenic nodules, absence of other organ involvement, no new sites of disease. PD: appearance of new lesion more than 1.5cm in any axis, at least 50% increase from nadir in SPD/longest diameter of previous lesion/node. Data censored on date of last adequate tumor assessment in subjects with no event, started new anti-cancer therapy/had 2/more missing assessments. Here, '99999'=due to no subject with PD/death, median and full range could not be estimated.

End point type	Secondary

End point timeframe:

First response (CR or PR) to date of PD, start of new anti-cancer therapy, discontinuation from the study, censoring date or death due to any cause, whichever occurred first (maximum up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	0[3]	3[4]	
Units: Months				
median (full range (min-max))	1.81 (1.81 to 1.81)	(to)	99999 (99999 to 99999)	

Notes:

[3] - Due to zero number of subject who had events, median and full range were not estimable.

[4] - All 3 subjects who achieved OR were not observed to have PD or death on study

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR) as Assessed by Investigator per Lugano Response Classification Criteria

End point title	Time to Tumor Response (TTR) as Assessed by Investigator per Lugano Response Classification Criteria

End point description:

TTR was defined for subjects who achieved objective response as time from randomization to first documentation of objective tumor response (CR or PR) that was subsequently confirmed. CR was defined as a score of 1 (no uptake above background), 2 (uptake <= mediastinum), or 3 (uptake <mediastinum but <=liver) with or without a residual mass on PET 5-PS, for lymph nodes and extralymphatic sites; no new lesions; no evidence of FDG-avid disease in bone marrow. PR was defined as >=50% decrease in SPD of up to six of the largest dominant lymph nodes, no increase in size of other nodes, liver, or spleen volume, a >=50% decrease in SPD of hepatic and splenic nodules, absence of other organ involvement, and no new sites of disease. Here, “N”: subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From the date of randomization to the first documentation of objective response (CR or PR) (maximum up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	0[5]	3	
Units: Months				
median (full range (min-max))	1.8 (1.8 to 1.8)	(to)	1.9 (1.7 to 2.6)	

Notes:

[5] - Due to zero number of subject who achieved OR, median and full range were not estimable.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate as Assessed by the Investigator per Lugano Response Classification Criteria

End point title	Disease Control Rate as Assessed by the Investigator per Lugano Response Classification Criteria

End point description:

Disease control rate was defined as percentage of subjects with disease control. Disease Control (DC) was defined as the best overall response of CR, PR, or stable disease (SD). CR: score of 1 (no uptake above background), 2 (uptake <= mediastinum), or 3 (uptake less than <mediastinum but <=liver) with or without a residual mass on PET 5-PS, for lymph nodes and extralymphatic sites; no new lesions; no evidence of FDG-avid disease in bone marrow. PR: >=50% decrease in SPD of up to six of the largest dominant lymph nodes, no increase in size of other nodes, liver, or spleen volume, a >=50% decrease in SPD of hepatic and splenic nodules, absence of other organ involvement, and no new sites of disease. SD: <50% decrease in SDP of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease met. To qualify as a best overall response of SD, at least one SD assessment must be observed >=6 weeks after start date and before disease progression. FAS analysed.

End point type	Secondary

End point timeframe:

From the date of randomization to the first documentation of PD, study discontinuation, start of new anti-cancer therapy or death due to any cause, whichever occurred first (maximum up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	11	
Units: Percentage of subjects				
number (confidence interval 95%)	22.2 (2.8 to 60.0)	0 (0 to 33.6)	36.4 (10.9 to 69.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) as Assessed by the Investigator per Lugano Response Classification Criteria

End point title	Progression-Free Survival (PFS) as Assessed by the

	Investigator per Lugano Response Classification Criteria

End point description:

Investigator assessed PFS was defined as time (in months) from date of randomization to the first documentation of disease progression or death (due to any cause), whichever occurred first. PFS data was censored on the date of the last adequate tumor assessment for subjects who had no an event (PD or death), for subjects who start a new anti-cancer therapy prior to an event or for subjects with an event after 2 or more missing or inadequate post-baseline tumor assessment. Subjects without an adequate baseline or post-baseline tumor assessment were censored on the date of randomization unless death occurred on or before the time of the second planned tumor assessment in which case the death was considered as an event. FAS analysed. Here, '99999' signifies that due to small number of subjects who had event, 95% CI was not estimable.

End point type	Secondary

End point timeframe:

From the date of randomization to progression of disease, study discontinuation, censoring date or death due to any cause, whichever occurred first (up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	11	
Units: Months				
median (confidence interval 95%)	1.8 (0.6 to 3.5)	1.5 (0.3 to 1.8)	2.7 (1.3 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was defined as the time (in months) from the date of randomization to the date of death due to any cause. Subjects last known to be alive were censored at date of last contact. Analysis was performed using Kaplan-Meier method. Full analysis set population included all subjects who were randomised in the study. Here, '99999' signifies that due to small number of subjects who had event, 95% CI was not estimable.

End point type	Secondary

End point timeframe:

From the date of randomization to discontinuation from the study or death, whichever occurred first (maximum up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	11	
Units: Months				
median (confidence interval 95%)	14.8 (0.9 to	4.0 (0.3 to	5.2 (1.3 to	

99999)	11.3)	99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration Verses Time Summary of Avelumab

End point title	Concentration Verses Time Summary of Avelumab

End point description:

Avelumab pharmacokinetic concentration analysis set included all subjects who received at least 1 dose of study drug and who had at least 1 post-dose concentration measurement above the lower limit of quantitation for avelumab. Here, '9999' signifies data not available as none of the subjects were evaluable at specified time point, and '99999' signifies that due to single subject, standard deviation could not be calculated at specified time point. Here, "n": subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

1 hour Post dose Day 2 Cycle 1, 144 hour Post dose Day 8 of Cycle 1, 0 hour Post dose Day 16 of Cycle 1, Day 1 of Cycle 4 and Cycle 6

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	11	
Units: micrograms per milliliter (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 2;(n=7,7,10)	183.29 (± 83.809)	198.43 (± 29.387)	193.30 (± 29.702)	
Cycle 1 Day 8; (n=8,8,10)	75.14 (± 21.357)	68.44 (± 18.553)	65.33 (± 17.913)	
Cycle 1 Day 16; (n=7,4,9)	25.33 (± 13.197)	26.53 (± 9.237)	19.36 (± 7.810)	
Cycle 4 Day 1;(n=2,1,4)	25.00 (± 4.667)	62.00 (± 99999)	120.88 (± 165.187)	
Cycle 6 Day 1; (n=0,1,4)	9999 (± 9999)	7.57 (± 99999)	39.43 (± 18.327)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-Drug Antibodies (ADA) Against Avelumab by Never and Ever Positive Status

End point title	Number of Subjects With Anti-Drug Antibodies (ADA) Against

	Avelumab by Never and Ever Positive Status

End point description:

ADA never-positive was defined as no positive ADA results at any time point. ADA ever-positive was defined as at least one positive ADA result at any time point. Avelumab immunogenicity analysis set included subjects who had at least 1 ADA sample collected for avelumab.

End point type	Secondary

End point timeframe:

Baseline: 2 hours pre-dose of first dose of avelumab, Post baseline: post first dose up to up to 30 Days after the end of treatment (maximum up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	11	
Units: Subjects				
Baseline: ADA ever-positive	0	0	1	
Baseline: ADA never-positive	8	9	10	
Post Baseline: ADA ever-positive	0	0	0	
Post Baseline: ADA never-positive	8	9	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-Drug Antibodies (ADA) Against Rituximab by Never and Ever Positive Status

End point title	Number of Subjects With Anti-Drug Antibodies (ADA) Against Rituximab by Never and Ever Positive Status[6]

End point description:

ADA never-positive was defined as no positive ADA results at any time point. ADA ever-positive was defined as at least one positive ADA result at any time point. Rituximab immunogenicity analysis set included subjects who had at least 1 ADA sample collected for rituximab.

End point type	Secondary

End point timeframe:

From the date of first study treatment up to 30 Days after the end of treatment (maximum up to 36 months)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only in the reporting arms identified

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Bendamustine+Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: Subjects				
ADA ever-positive	0	0		
ADA never-positive	8	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Anti-Drug Antibodies (ADA) Against Utomilumab by Never and Ever Positive Status

End point title	Number of Subjects With Anti-Drug Antibodies (ADA) Against Utomilumab by Never and Ever Positive Status[7]

End point description:

ADA never-positive was defined as no positive ADA results at any time point. ADA ever-positive was defined as at least one positive ADA result at any time point. Utomilumab immunogenicity analysis set included subjects who had at least 1 ADA sample collected for utomilumab.

End point type	Secondary

End point timeframe:

From the date of first study treatment up to 30 Days after the end of treatment (maximum up to 36 months)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only in the reporting arms identified

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Subjects				
ADA ever-positive	1	2		
ADA never-positive	7	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Neutralizing Antibodies (nAb) Against Avelumab by Never and Ever Positive Status

End point title	Number of Subjects With Neutralizing Antibodies (nAb) Against Avelumab by Never and Ever Positive Status

End point description:

nAb never-positive was defined as no positive nAb results at any time point and nAb ever-positive was defined as at least one positive nAb result at any time point. Data for this endpoint was not collected since there was no subjects with post-baseline ADA ever positive sample for avelumab.

End point type	Secondary

End point timeframe:

From the date of first study treatment up to 30 Days after the end of treatment (maximum up to 36 months)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: Subjects				

Notes:

[8] - There was no subjects with post-baseline ADA ever positive sample for avelumab.

[9] - There was no subjects with post-baseline ADA ever positive sample for avelumab.

[10] - There was no subjects with post-baseline ADA ever positive sample for avelumab.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Neutralizing Antibodies (nAb) Against Rituximab by Never and Ever Positive Status

End point title	Number of Subjects With Neutralizing Antibodies (nAb) Against Rituximab by Never and Ever Positive Status[11]

End point description:

nAb never-positive was defined as no positive nAb results at any time point and nAb ever-positive was defined as at least one positive nAb result at any time point. Data for this this endpoint was not collected since there was no subjects with rituximab ADA ever positive sample.

End point type	Secondary

End point timeframe:

From the date of first study treatment up to 30 Days after the end of treatment (maximum up to 36 months)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only in the reporting arms identified

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Bendamustine+Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Subjects				

Notes:

[12] - There was no subject with rituximab ADA ever positive sample.

[13] - There was no subject with rituximab ADA ever positive sample.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Neutralizing Antibodies (nAb) Against Utomilumab by Never and Ever Positive Status

End point title	Number of Subjects With Neutralizing Antibodies (nAb) Against Utomilumab by Never and Ever Positive Status[14]

End point description:

nAb never-positive was defined as no positive nAb results at any time point and nAb ever-positive was defined as at least one positive nAb result at any time point. Utomilumab immunogenicity analysis set included subjects from the safety analysis set who had at least one ADA/nAb sample collected for utomilumab. Here, N=subjects who were ADA positive and whose samples were further analysed for nAb.

End point type	Secondary

End point timeframe:

From the date of first study treatment up to 30 Days after the end of treatment (maximum up to 36 months)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analyzed only in the reporting arms identified

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: Subjects				
nAb ever-positive	0	0		
nAb never-positive	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Programmed Death Receptor-1 Ligand-1 (PD-L1) Biomarker Expression in Tumor and Immune Cells as Assessed by Immunohistochemistry (IHC) at Baseline

End point title	Programmed Death Receptor-1 Ligand-1 (PD-L1) Biomarker Expression in Tumor and Immune Cells as Assessed by Immunohistochemistry (IHC) at Baseline

End point description:

Percentage of Tumor and Immune Cells as Assessed by Immunohistochemistry (IHC) at Baseline. FAS analysed. Here, N=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Screening (prior to first dose of study treatment)

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	8	6	
Units: Percentage of cells staining positive				
median (full range (min-max))				

Tumor Cells (membrane)	0 (0 to 5)	0.5 (0.0 to 10.0)	0 (0 to 30)	
Immune Cells	7.5 (0.0 to 30.0)	7.5 (0.0 to 70.0)	17.5 (0.0 to 50.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Minimal Residual Disease Burden (MRD) Positive, Negative and Not Evaluable (NE) Status

End point title	Number of Subjects With Minimal Residual Disease Burden (MRD) Positive, Negative and Not Evaluable (NE) Status

End point description:

Number of participants with MRD positive, negative and not evaluable status were reported in this endpoint. Safety analysis set population included all subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycle 3, 6, 9, 12 and 18

End point values	Avelumab+Rituximab+Utomilumab	Avelumab+Azacitidine+Utomilumab	Avelumab+Bendamustine+Rituximab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	11	
Units: Subjects				
Baseline: Positive	3	1	3	
Baseline: Negative	0	0	2	
Baseline: NE	5	8	6	
Cycle 3 Day 1: Positive	3	1	1	
Cycle 3 Day 1: Negative	0	0	3	
Cycle 3 Day 1: NE	2	1	1	
Cycle 6 Day 1: Positive	0	1	0	
Cycle 6 Day 1: Negative	0	0	2	
Cycle 6 Day 1: NE	0	0	2	
Cycle 9 Day 1: Positive	0	0	0	
Cycle 9 Day 1: Negative	0	0	1	
Cycle 9 Day 1: NE	0	0	2	
Cycle 12 Day 1: Positive	0	0	0	
Cycle 12 Day 1: Negative	0	0	1	
Cycle 12 Day 1: NE	0	0	2	
Cycle 18 Day 1: Positive	0	0	0	
Cycle 18 Day 1: Negative	0	0	0	
Cycle 18 Day 1: NE	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to follow up (36 months)

Adverse event reporting additional description:

Same event may appear as AE and serious AE, what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during study. Safety analysis set population included all subjects who were randomised in the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Avelumab+Rituximab+Utomilumab

Reporting group description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycle 1 and 2, if well tolerated than continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 mg/m^2 IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab tolerated well than it continued to administer on Day 1 in Cycle 3 and in all subsequent cycles until the subject no longer received clinical benefit. Each treatment cycle was of 28 days.

Reporting group title	Avelumab+Bendamustine+Rituximab

Reporting group description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycle 1 and 2, if well tolerated than continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Rituximab 375 mg/m^2 IV infusion was administered on Day 1 of each treatment cycle (maximum of 8 cycles), along with 90 mg/m^2 IV infusion of bendamustine on Day 2 and Day 3 of each treatment cycle in Cycles 1 and 2. If the dose of bendamustine tolerated well than it continued to administer on Day 1 and Day 2 in Cycle 3 and in all subsequent cycles for a maximum of 6 cycles. Each treatment cycle was of 28 days.

Reporting group title	Avelumab+Azacitidine+Utomilumab

Reporting group description:

Avelumab 10 mg/kg IV infusion was administered every 2 weeks on Day 2 and Day 16 of Cycle 1 and 2, if well tolerated than continued on Day 1 and Day 15 in Cycle 3 and all subsequent cycles, until the subject no longer received clinical benefit. Azacitidine 40 mg/m^2 sub-cutaneous (SC) dose was administered on Day 1 to 5 of each treatment cycle, along with fixed dose of 100 mg IV infusion of utomilumab on Day 2 of each treatment cycle in Cycles 1 and 2. If the dose of utomilumab tolerated well, than it continued to administer on Day 1 in Cycle 3 and in all subsequent cycles until the subject no longer received clinical benefit. Each treatment cycle was of 28 days.

Serious adverse events	Avelumab+Rituximab+Utomilumab	Avelumab+Bendamustine+Rituximab	Avelumab+Azacitidine+Utomilumab
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	7 / 11 (63.64%)	6 / 9 (66.67%)
number of deaths (all causes)	4	6	8
number of deaths resulting from adverse events	2	1	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			

subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Disease progression			

subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
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 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Laryngeal oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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 failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	2 / 2
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Herpes zoster			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (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
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (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
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Septic shock			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (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 infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (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
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
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 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
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	Avelumab+Rituximab+Utomilumab	Avelumab+Bendamustine+Rituximab	Avelumab+Azacitidine+Utomilumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	11 / 11 (100.00%)	9 / 9 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Hypotension			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Superior vena cava syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Chills			
subjects affected / exposed	3 / 8 (37.50%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	5	1	1
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	4 / 11 (36.36%)	1 / 9 (11.11%)
occurrences (all)	1	6	1
Generalised oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Influenza like illness			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Injection site erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Oedema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	3 / 8 (37.50%)	3 / 11 (27.27%)	1 / 9 (11.11%)
occurrences (all)	4	4	1
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Cough			

subjects affected / exposed	2 / 8 (25.00%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	3	2	1
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Dyspnoea exertional			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Pulmonary oedema			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Confusional state			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Amylase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Bilirubin conjugated increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood alkaline phosphatase			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	2 / 9 (22.22%)
occurrences (all)	0	2	2
Blood bilirubin increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Blood calcium			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood chloride increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 8 (25.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	3	0	2
Blood creatinine increased			

subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	0	6	1
Blood triglycerides increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	0	3	2
Haemoglobin decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lipase decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 8 (0.00%)	3 / 11 (27.27%)	1 / 9 (11.11%)
occurrences (all)	0	11	1
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	0 / 9 (0.00%)
occurrences (all)	0	9	0
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
White blood cell count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	4	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	0	2	2
Infusion related reaction			

subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Transfusion reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Sinus bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Head discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Lethargy			

subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Taste disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 8 (25.00%)	4 / 11 (36.36%)	2 / 9 (22.22%)
occurrences (all)	3	8	2
Leukopenia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	0 / 9 (0.00%)
occurrences (all)	0	3	0
Lymph node pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	2 / 8 (25.00%)	5 / 11 (45.45%)	1 / 9 (11.11%)
occurrences (all)	5	16	1
Thrombocytopenia			
subjects affected / exposed	1 / 8 (12.50%)	3 / 11 (27.27%)	0 / 9 (0.00%)
occurrences (all)	1	8	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Dry eye			

subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Abdominal distension			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	4 / 11 (36.36%)	5 / 9 (55.56%)
occurrences (all)	1	5	6
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	3	2	1
Hiatus hernia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	4 / 11 (36.36%)	2 / 9 (22.22%)
occurrences (all)	2	6	3
Oesophageal obstruction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	0 / 9 (0.00%)
occurrences (all)	0	2	0

Toothache			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
Rash			
subjects affected / exposed	1 / 8 (12.50%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	2	2	3
Rash erythematous			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	1	0	1
Haematuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Microalbuminuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Nocturia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	5	0
Renal failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Primary hypothyroidism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	2 / 8 (25.00%)	0 / 11 (0.00%)	3 / 9 (33.33%)
occurrences (all)	2	0	4
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Joint range of motion decreased			

subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
Myalgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	1	2	0
Herpes zoster			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 8 (25.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	2	1	0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 8 (37.50%)	3 / 11 (27.27%)	0 / 9 (0.00%)
occurrences (all)	3	4	0
Hypercalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypermagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypernatraemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypocalcaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			

subjects affected / exposed	1 / 8 (12.50%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	3	2	1
Hypomagnesaemia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	1	2	0
Hypophosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	0 / 9 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2017	Futility Interim Analysis added in Phase 1b to allow for early stopping of any treatment arm for futility.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data for Phase 3 endpoints were not collected as study was terminated early and phase 3 was not conducted.

Notes: