



Clinical trial results:

A PHASE II STUDY OF ATEZOLIZUMAB WITH RITUXIMAB, GEMCITABINE AND OXALIPLATIN IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA WHO ARE NOT CANDIDATES FOR HIGH-DOSE THERAPY.

Summary

EudraCT number	2016-002654-21
Trial protocol	GB
Global end of trial date	31 January 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	RHMCAN1219
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03422523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation
Sponsor organisation address	Tremona Road, Southampton, United Kingdom, SO17 1BJ
Public contact	Karen Martin, Southampton Clinical Trials Unit, +44 023 8120 3507 , k.s.martin@soton.ac.uk
Scientific contact	Karen Martin, Southampton Clinical Trials Unit, +44 023 8120 3507 , k.s.martin@soton.ac.uk

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	20 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2021
Global end of trial reached?	Yes
Global end of trial date	31 January 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To document the durable anti-tumour activity of R-GemOx-Atezo in patients with relapsed or refractory DLBCL

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 54
Worldwide total number of subjects	54
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	39
From 65 to 84 years	14
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Between July 2018 and June 2020, ARGO recruited 53 patients (Arm A: 12 Arm B: 42). At this point, recruitment was stopped prior to the planned interim assessment. The trial protocol stipulated that if PFS at 1 year is less than 25%, then a trial would not warrant further investigation.

Pre-assignment

Screening details:

Inclusion Criteria:

Histologically proven CD20 +ve diffuse large B-cell lymphoma with sufficient diagnostic material, obtained either at diagnosis or relapse (the latter is preferable) that is available to forward to the Haematological Malignancies Diagnostic Service (HMDS) for gene expression profiling and central pathology review.

Period 1

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

Blinding implementation details:

Open labeled

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A Control

Arm description:

6 Cycles of R-GemOx (Rituximab, Gemcitabine, and Oxaliplatin). Each cycle lasts 14 days

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

375 mg/m² on day 1 (cycle 1), 1400 mg/m² on day 1 (cycle 2-6)

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

1000 mg/m² on day 1 (cycle 1-6)

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

100 mg/m² on day 1 (cycle 1-6)

Investigational medicinal product name	G-CSF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details: 30MU on days 5-11 (cycle 1-6)	
Arm title	Arm B Experimental
Arm description:	
Treatment arm	
Arm type	Experimental
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
375 mg/m ² on day 1 (cycle 1) - infusion form, 1400 mg/m ² on day 1 (cycle 2-6) - subcutaneous form	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
1000 mg/m ² on day 1 (cycle 1-6)	
Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
100 mg/m ² on day 1 (cycle 1-6)	
Investigational medicinal product name	G-CSF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
30MU on days 5-11 (cycle 1-6)	
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use
Dosage and administration details:	
840 mg/m ² on day 1 (cycle 2-cycle 6)	
Maintenance therapy with Atezolizumab (IV) 840mg to be given every 21 days for 8 cycles	

Number of subjects in period 1	Arm A Control	Arm B Experimental
Started	12	42
Completed	0	3
Not completed	12	39
Stopped by sponsor	7	12
Death	5	27

Baseline characteristics

Reporting groups

Reporting group title	Arm A Control
Reporting group description: 6 Cycles of R-GemOx (Rituximab, Gemcitabine, and Oxaliplatin). Each cycle lasts 14 days	
Reporting group title	Arm B Experimental
Reporting group description: Treatment arm	

Reporting group values	Arm A Control	Arm B Experimental	Total
Number of subjects	12	42	54
Age categorical Units: Subjects			
Adults (18-64 years)	7	32	39
From 65-84 years	5	9	14
Age over 85 years	0	1	1
Age continuous Units: years			
median	69.5	74	
inter-quartile range (Q1-Q3)	61 to 73.5	68 to 76	-
Gender categorical Units: Subjects			
Female	5	17	22
Male	7	25	32
IPI Score at study entry – n (%) Units: Subjects			
IPI score 0	0	0	0
IPI score 1	1	4	5
IPI score 2	4	11	15
IPI score 3	5	16	21
IPI score 4	2	10	12
IPI score 5	0	1	1
ECOG Performance Status – n (%) Units: Subjects			
0 – Fully active	4	17	21
1 – Restricted in physically strenuous activity	6	22	28
2 – Capable of all self-care but out of work	2	1	3
3 – Capable of only limited self-care	0	2	2
Refractory or relapse patient – n (%) Units: Subjects			
Refractory	7	24	31
Relapse	5	18	23
Cell of Origin - n (%) Units: Subjects			
ABC	5	13	18
GCB	6	14	20

Unclassified	0	4	4
Fail	1	5	6
Unavailable	0	6	6

End points

End points reporting groups

Reporting group title	Arm A Control
Reporting group description:	6 Cycles of R-GemOx (Rituximab, Gemcitabine, and Oxaliplatin). Each cycle lasts 14 days
Reporting group title	Arm B Experimental
Reporting group description:	
Treatment arm	

Primary: PFS Kaplan-Meier estimates - Median PFS

End point title	PFS Kaplan-Meier estimates - Median PFS
End point description:	

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

End point timeframe:

Progression-free survival will be measured from the day of randomisation until progression or death from any cause. Patients who did not progress or die were censored at their date of last follow up.

End point values	Arm A Control	Arm B Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	41		
Units: months				
median (confidence interval 90%)	3.5 (1.4 to 7)	4.3 (3.4 to 6.9)		

Statistical analyses

Statistical analysis title	Median PFS
Comparison groups	Arm B Experimental v Arm A Control
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
Parameter estimate	Median PFS
Point estimate	4.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	3.4
upper limit	6.9

Notes:

[1] - Arm A was a reference arm, the study was not powered for a direct comparison between groups. Therefore the below analysis is just for Arm B (41 patients)

Primary: PFS Kaplan-Meier estimates - PFS at 12 months from study registration

End point title	PFS Kaplan-Meier estimates - PFS at 12 months from study registration
-----------------	---

End point description:

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

End point timeframe:

From date of randomisation until progression or death from any cause. Patients who did not progress or die were censored at their date of last follow up.

End point values	Arm A Control	Arm B Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	41 ^[2]		
Units: percent				
number (confidence interval 95%)	16.7 (2.7 to 41.3)	15.1 (6.1 to 27.7)		

Notes:

[2] - Excluded ineligible participant

Statistical analyses

Statistical analysis title	PFS at 12 months from study registration
Comparison groups	Arm B Experimental v Arm A Control
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
Parameter estimate	PFS at 12 months from study registration
Point estimate	15.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	7.2
upper limit	25.5

Notes:

[3] - Arm A was a reference arm, the study was not powered for a direct comparison between groups. Therefore the below analysis is just for Arm B (41 patients)

Secondary: OS Kaplan-Meier estimates - Median OS

End point title	OS Kaplan-Meier estimates - Median OS
-----------------	---------------------------------------

End point description:

Values of 99 represent values that can't be estimated

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

End point timeframe:

Overall survival will be measured from the day of randomisation to the date of death from any cause. Patients who do not die will be censored at their date of last follow up.

End point values	Arm A Control	Arm B Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	41		
Units: months				
median (confidence interval 90%)	99 (5.1 to 99)	13.5 (8 to 17.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: OS Kaplan-Meier estimates - OS at 12 months from study registration

End point title	OS Kaplan-Meier estimates - OS at 12 months from study registration
-----------------	---

End point description:

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

End point timeframe:

Overall survival will be measured from the day of randomisation to the date of death from any cause. Patients who do not die will be censored at their date of last follow up.

End point values	Arm A Control	Arm B Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	41 ^[4]		
Units: percent				
number (confidence interval 95%)	58.3 (27 to 80.1)	56.1 (39.7 to 69.6)		

Notes:

[4] - Excluded ineligible participant

Statistical analyses

No statistical analyses for this end point

Secondary: Overall toxicity by CTCAE Grade for AEs which occurred during treatment

End point title	Overall toxicity by CTCAE Grade for AEs which occurred during treatment
-----------------	---

End point description:

Adverse events – n

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

End point timeframe:

An AE is considered in the treatment period if it is between treatment start date and week 17 (day 119 if randomisation if day 0)

End point values	Arm A Control	Arm B Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12 ^[5]	42 ^[6]		
Units: participant				
CTCAE 4.03 Grade 1	0	0		
CTCAE 4.03 Grade 2	5	11		
CTCAE 4.03 Grade 3	5	21		
CTCAE 4.03 Grade 4	2	8		
CTCAE 4.03 Grade 5	0	2		

Notes:

[5] - The worst grade is used when more than one grade is available for a patient

[6] - The worst grade is used when more than one grade is available for a patient

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.0
--------------------	------

Reporting groups

Reporting group title	Arm A
-----------------------	-------

Reporting group description: -

Reporting group title	Arm B
-----------------------	-------

Reporting group description: -

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	30 / 42 (71.43%)	
number of deaths (all causes)	5	30	
number of deaths resulting from adverse events	0	3	
Vascular disorders			
Orthostatic Hypotension	Additional description: Orthostatic Hypotension		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hospitalisation	Additional description: Hospitalisation		
subjects affected / exposed	0 / 12 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise	Additional description: Malaise		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease Progression	Additional description: Disease Progression		

subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Swelling	Additional description: Peripheral Swelling		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse Drug Reaction	Additional description: Adverse Drug Reaction		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Cardiac Chest Pain	Additional description: Non-Cardiac Chest Pain		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	0 / 12 (0.00%)	13 / 42 (30.95%)	
occurrences causally related to treatment / all	0 / 0	11 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia	Additional description: Asthenia		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngospasm	Additional description: Laryngospasm		

subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: Pneumonitis		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac disorders			
Atrial Fibrillation	Additional description: Atrial Fibrillation		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter	Additional description: Atrial Flutter		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope	Additional description: Syncope		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile Neutropenia	Additional description: Febrile Neutropenia		
subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea	Additional description: Diarrhoea		

subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Haemorrhage	Additional description: Rectal Haemorrhage		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena	Additional description: Melaena		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain	Additional description: Abdominal Pain		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis	Additional description: Cholecystitis		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury	Additional description: Acute Kidney Injury		
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
	Additional description: Muscular Weakness		
	subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)
	occurrences causally related to treatment / all	1 / 1	0 / 0
Neck Pain	Additional description: Neck Pain		
	subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Back Pain	Additional description: Back Pain		
	subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Infections and infestations			
	Additional description: Device Related Sepsis		
	subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
Klebsiella Bacteraemia	Additional description: Klebsiella Bacteraemia		
	subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Infection	Additional description: Infection		
	subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)
	occurrences causally related to treatment / all	0 / 0	1 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Influenza	Additional description: Influenza		
	subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)
	occurrences causally related to treatment / all	0 / 0	0 / 3
	deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis	Additional description: Sepsis		
	subjects affected / exposed	1 / 12 (8.33%)	2 / 42 (4.76%)
	occurrences causally related to treatment / all	0 / 1	2 / 2
	deaths causally related to treatment / all	0 / 0	0 / 0

Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	0 / 12 (0.00%)	4 / 42 (9.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Lower Respiratory Tract Infection	Additional description: Lower Respiratory Tract Infection		
subjects affected / exposed	0 / 12 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased Appetite	Additional description: Decreased Appetite		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Lysis Syndrome	Additional description: Tumour Lysis Syndrome		
subjects affected / exposed	0 / 12 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	42 / 42 (100.00%)	
Vascular disorders			
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	
occurrences (all)	1	2	
Flushing	Additional description: Flushing		
subjects affected / exposed	1 / 12 (8.33%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Phlebitis	Additional description: Phlebitis		

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Surgical and medical procedures			
Ureteric calculus removal	Additional description: Ureteric calculus removal		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
General disorders and administration site conditions			
Mucosal inflammation	Additional description: Mucosal inflammation		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	2 / 42 (4.76%) 2	
Fatigue	Additional description: Fatigue		
subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 4	22 / 42 (52.38%) 26	
Extravasation	Additional description: Extravasation		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	8 / 42 (19.05%) 10	
Asthenia	Additional description: Asthenia		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 42 (2.38%) 2	
Respiratory, thoracic and mediastinal disorders			
Productive cough	Additional description: Productive cough		
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	3 / 42 (7.14%) 3	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	9 / 42 (21.43%) 11	
Cough	Additional description: Cough		
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	6 / 42 (14.29%) 6	
Sinus congestion	Additional description: Sinus congestion		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Hiccups	Additional description: Hiccups		

subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Psychiatric disorders			
Hallucination	Additional description: Hallucination		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	1 / 12 (8.33%)	6 / 42 (14.29%)	
occurrences (all)	1	10	
Blood creatinine increased	Additional description: Blood creatinine increased		
subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	4	
Blood magnesium decreased	Additional description: Blood magnesium decreased		
subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Gamma-glutamyltransferase increased	Additional description: Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Weight decreased	Additional description: Weight decreased		
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	1 / 12 (8.33%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Blood alkaline phosphatase increased	Additional description: Blood alkaline phosphatase increased		
subjects affected / exposed	2 / 12 (16.67%)	8 / 42 (19.05%)	
occurrences (all)	2	10	
Injury, poisoning and procedural complications			
Infusion related reaction	Additional description: Infusion related reaction		
subjects affected / exposed	1 / 12 (8.33%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Nervous system disorders			
Neurotoxicity	Additional description: Neurotoxicity		

subjects affected / exposed	2 / 12 (16.67%)	1 / 42 (2.38%)	
occurrences (all)	2	1	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	6 / 12 (50.00%)	15 / 42 (35.71%)	
occurrences (all)	10	20	
Peripheral sensory neuropathy	Additional description: Peripheral sensory neuropathy		
subjects affected / exposed	0 / 12 (0.00%)	6 / 42 (14.29%)	
occurrences (all)	0	14	
Headache	Additional description: Headache		
subjects affected / exposed	1 / 12 (8.33%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	3 / 12 (25.00%)	7 / 42 (16.67%)	
occurrences (all)	3	8	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	0 / 12 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Lethargy	Additional description: Lethargy		
subjects affected / exposed	1 / 12 (8.33%)	5 / 42 (11.90%)	
occurrences (all)	4	6	
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	8 / 12 (66.67%)	25 / 42 (59.52%)	
occurrences (all)	17	93	
Anaemia	Additional description: Anaemia		
subjects affected / exposed	2 / 12 (16.67%)	11 / 42 (26.19%)	
occurrences (all)	3	17	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	1 / 12 (8.33%)	8 / 42 (19.05%)	
occurrences (all)	1	11	
Haematotoxicity	Additional description: Haematotoxicity		
subjects affected / exposed	1 / 12 (8.33%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tympanic membrane perforation	Additional description: Tympanic membrane perforation		

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3	6 / 42 (14.29%) 6	
Vomiting	Additional description: Vomiting		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	9 / 42 (21.43%) 19	
Nausea	Additional description: Nausea		
subjects affected / exposed occurrences (all)	6 / 12 (50.00%) 10	19 / 42 (45.24%) 31	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 4	17 / 42 (40.48%) 26	
Constipation	Additional description: Constipation		
subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 5	14 / 42 (33.33%) 16	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	3 / 42 (7.14%) 3	
Gastritis	Additional description: Gastritis		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash		
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	7 / 42 (16.67%) 9	
Decubitus ulcer	Additional description: Decubitus ulcer		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 42 (2.38%) 1	
Alopecia	Additional description: Alopecia		
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	4 / 42 (9.52%) 4	
Hyperhidrosis	Additional description: Hyperhidrosis		

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	4 / 42 (9.52%) 4	
Renal and urinary disorders			
Haematuria	Additional description: Haematuria		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Pollakiuria	Additional description: Pollakiuria		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Dysuria	Additional description: Dysuria		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	3 / 42 (7.14%) 5	
Musculoskeletal and connective tissue disorders			
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2	0 / 42 (0.00%) 0	
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	4 / 42 (9.52%) 4	
Bone pain	Additional description: Bone pain		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 42 (2.38%) 1	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	4 / 42 (9.52%) 4	
Back pain	Additional description: Back pain		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	4 / 42 (9.52%) 4	
Musculoskeletal pain	Additional description: Musculoskeletal pain		
subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0	
Infections and infestations			

Oral candidiasis subjects affected / exposed occurrences (all)	Additional description: Oral candidiasis	
	1 / 12 (8.33%) 1	1 / 42 (2.38%) 1
Rhinitis subjects affected / exposed occurrences (all)	Additional description: Rhinitis	
	1 / 12 (8.33%) 1	3 / 42 (7.14%) 4
Sinusitis subjects affected / exposed occurrences (all)	Additional description: Sinusitis	
	1 / 12 (8.33%) 1	0 / 42 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	Additional description: Cellulitis	
	1 / 12 (8.33%) 1	1 / 42 (2.38%) 1
Urinary tract infection subjects affected / exposed occurrences (all)	Additional description: Urinary tract infection	
	1 / 12 (8.33%) 1	1 / 42 (2.38%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Upper respiratory tract infection	
	0 / 12 (0.00%) 0	3 / 42 (7.14%) 4
Lower respiratory tract infection subjects affected / exposed occurrences (all)	Additional description: Lower respiratory tract infection	
	1 / 12 (8.33%) 1	3 / 42 (7.14%) 4
Metabolism and nutrition disorders		
	Additional description: Decreased appetite	
	2 / 12 (16.67%) 2	8 / 42 (19.05%) 8
Hypokalaemia subjects affected / exposed occurrences (all)	Additional description: Hypokalaemia	
	1 / 12 (8.33%) 1	2 / 42 (4.76%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2017	Minor changes as per MHRA request to contraceptive use and addition of serum magnesium in biochemistry tests. PI's to advise male participants about sperm conservation prior to treatment.
27 March 2018	Added transformed follicular to DLBCL to inclusion criteria Updated RSI information and versions of IBs for all IMPs. Wording of PET-CT requirements clarified, where PET/CT was used replaced with PET-CT. Removed text instructions to take Flow sample at diagnosis as this is not part of trial procedures. Update to Adverse Events of Special Interest section 7.5.4 Update Appendix 7 with Atezolizumab IB v10 guidance for the Management of Atezolizumab specific adverse events.
11 December 2018	References to data protection act removed throughout. Updates to trial procedures: <ul style="list-style-type: none">• Screening PET-CT window extended from within 28 days of treatment to within 42 days from treatment. (Also updated in section 5.1)• Bone marrow at screening now optional, investigators discretion as to whether it should be performed. Should still be performed if screening lab values are lower than expected to confirm eligibility on basis of bone marrow involvement. (Also updated in section 5.1)• Correction to wording, where 'registration' was written and it should have read 'randomisation' to occur following successful completion of screening stage.• Flow Samples collection window extended, can be taken up to 72 hours prior to day 1 of cycles where sample is to be collected. Now in line with the Streck sample window for collection. (Also updated in section 8.2)• Removal of instruction to randomise 3 days prior to treatment, this was an error. Randomisation to occur within 14 days of treatment.• Physical exam and ECOG performance status. To be taken within 48 hours of IMP administration.
11 December 2018	Updates to eligibility criteria: <ul style="list-style-type: none">• CD20 +ve diffuse large B-cell lymphoma (including transformation of previous low-grade lymphoma and primary mediastinal B-cell lymphoma)• Sufficient diagnostic material is now preferable, not mandatory, and age of blocks is 'ideally' within 6 months.• Clarification that patients can have received more than two prior lines of treatment.• Correction to the text where incorrectly it has been stated that male patients should use 'one form' of highly effective contraception and then listed acceptable forms which came as sets of two. This should have read 'two forms', so is now in line with the Patient Information Sheet (also corrected in section 7.5.6).• Creatinine clearance exclusion values made clearer that values below 60ml/min would be excluded, even with normal creatinine result.

11 December 2018	<p>Updates to section 5.1- Screening procedures updated to include new instructions for the tumour block requirements. These should 'ideally' be taken within 6 months of enrolment, previously it was stated they 'must be' taken within 6 months of enrolment. Sending of local pathology reports on the blocks where available to HMDS.</p> <p>Updates to section 6.8- Dose delays and modifications for toxicity Haematological toxicity-guided adjustments for immunochemotherapy, if platelets fall below 75 x 10⁹/L chemotherapy should be delayed. Previously this was below 100 x 10⁹/L and has been changed to be in line with exclusion criteria screening levels.</p>
11 December 2018	<p>Updates to section 9.2- Sample Size:</p> <ul style="list-style-type: none"> Removal of information about Case-Morgan design and inclusion of information relating to trial length. Minor wording updates to the flow diagram to clarify analysis will be on experimental arm patients. <p>Updates to 9.3 Statistical Analysis Plan (SAP):</p> <ul style="list-style-type: none"> Clarification of analysis populations, to now include 'efficacy safety population' <p>Appendix 7 - Management of atezolizumab-specific adverse events, updated to include new information from Roche regarding Immune related Nephritis as a known side effect, and its recommended management.</p>
11 December 2018	<p>Update to section 6.10- IMP storage so that it is in agreement with IB guidance.</p> <p>Update to Reference Safety Information:</p> <ul style="list-style-type: none"> New IB's and locations of RSI information Information to refer to the most up to date SmPC in place for the trials nIMP <p>Updates to section 8.3- Translational Blood Samples. Expanding the Streck sample description so that it is as detailed as that of Flow samples in section 8.2</p>
05 March 2019	<p>Update to RSI table – SmPC's for Gemcitabine and Oxaliplatin, and Atezolizumab IB updated from previous version.</p> <p>Guidelines added for permitted uses of single site radiotherapy post cycles in sections 5.3 and 5.9</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	ARGO was paused for recruitment in March 2020 due to the coronavirus pandemic. The trial never restated due to the decision of the DMEC in June 2020 to terminate the study.	-

Notes:

Limitations and caveats

None reported