Clinical trial results:
A Phase II, Multicenter, Open-Label Study of YM155 Plus Rituximab in Previously Treated Patients with CD20-Positive B Cell Non-Hodgkin's Lymphoma Who Are Ineligible for or Have Previously Received an Autologous Stem Cell Transplant

Summary

EudraCT number	2009-010777-20
Trial protocol	FR ES GB
Global end of trial date	23 June 2015

Results information

Result version number	v1 (current)
This version publication date	24 June 2016
First version publication date	24 June 2016

Trial information

Trial identification

Sponsor protocol code	155-CL-031

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01007292
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.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	05 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 March 2013
Global end of trial reached?	Yes
Global end of trial date	23 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine objective response rate (ORR) (complete remission [CR] + partial remission [PR]) per modified International Working Group (IWG) Revised Response Criteria for Malignant Lymphomas.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	43
EEA total number of subjects	32

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	22
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multicenter study was conducted at 35 sites; 16 sites in the United States (US), 8 sites in France, 6 sites in Spain, and 5 sites in the United Kingdom (UK).

Pre-assignment

Screening details:

A total of 52 participants were screened, 43 enrolled, 41 received treatment. Eligible participants received YM155 5.0 mg/m^2/day and Rituximab 375 mg/m^2. A participant was considered as having completed treatment if the patient met one of the discontinuation criteria.

Period 1

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

Blinding implementation details:

This section is not applicable since this is an open-label study.

Arms

Arm title	YM155 plus rituximab

Arm description:

Participants were administered YM155 and rituximab during 14-day cycles. Rituximab (375 mg/m^2) was administered weekly on days 1 and 8 during cycles 1 to 4, repeated every 10 cycles (i.e., cycles 11-14, 21-24, etc.). YM155 (5 mg/m^2 per day intravenously (IV)) was administered by continuous infusion for 168 hours via a central line, port or peripherally-inserted central catheter (PICC) from days 1 to 8 of each cycle.

Arm type	Experimental
Investigational medicinal product name	YM155
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered YM155 during 14-day cycles. YM155 (5 mg/m^2 per day IV) was administered by continuous infusion for 168 hours via a central line, port or PICC from days 1 to 8 of each cycle. During cycles in which both YM155 and rituximab were administered, the YM155 infusion on day 1 was to be initiated within 1 hour following completion of the rituximab infusion. Each dose of YM155 was based upon body surface area (BSA), calculated using actual weight for participants with body mass index (BMI) < 30 kg/m^2 and adjusted (vs. actual) body weight for participants with BMI ≥ 30 kg/m^2. If a participant gained weight leading to a BMI increase from < 30 to ≥ 30 kg/m^2, then BSA was recalculated based upon the new, adjusted weight to determine if the YM155 dose should be increased. If the YM155 dose actually decreased (compared to original dose) when using the adjusted BSA, then the original dose of YM155 should have been utilized.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	Rituxan, Mabthera
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants were administered rituximab during 14-day cycles. Rituximab (375 mg/m^2) was administered weekly on days 1 and 8 during cycles 1 to 4, repeated every 10 cycles (i.e., cycles 11-14, 21-24, etc.). On day 8, the rituximab infusion could have been initiated during, but no later than 1 hour following the completion of, the YM155 infusion. If the rituximab infusion was initiated prior to the end of the YM155 infusion, a separate peripheral line in a different anatomical location must have been used.

Number of subjects in period 1	YM155 plus rituximab
Started	43
Treated	41
Completed	34
Not completed	9
Enrolled but did not receive study drug	2
Ongoing participants	7

Baseline characteristics

Reporting groups	
Reporting group title	YM155 plus rituximab

Reporting group description:

Participants were administered YM155 and rituximab during 14-day cycles. Rituximab (375 mg/m^2) was administered weekly on days 1 and 8 during cycles 1 to 4, repeated every 10 cycles (i.e., cycles 11-14, 21-24, etc.). YM155 (5 mg/m^2 per day intravenously (IV)) was administered by continuous infusion for 168 hours via a central line, port or peripherally-inserted central catheter (PICC) from days 1 to 8 of each cycle.

Reporting group values	YM155 plus rituximab	Total	
Number of subjects	43	43	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	63		
standard deviation	± 13.7	-	
Gender categorical Units:			
Male	28	28	
Female	15	15	

End points

End points reporting groups

Reporting group title	YM155 plus rituximab

Reporting group description:

Participants were administered YM155 and rituximab during 14-day cycles. Rituximab (375 mg/m^2) was administered weekly on days 1 and 8 during cycles 1 to 4, repeated every 10 cycles (i.e., cycles 11-14, 21-24, etc.). YM155 (5 mg/m^2 per day intravenously (IV)) was administered by continuous infusion for 168 hours via a central line, port or peripherally-inserted central catheter (PICC) from days 1 to 8 of each cycle.

Primary: Objective Response Rate (ORR) (Confirmed Complete Remission/Confirmed Partial Remission)

End point title	Objective Response Rate (ORR) (Confirmed Complete Remission/Confirmed Partial Remission)[1]

End point description:

ORR was based on percentage of participants with confirmed CR/confirmed PR investigator assessed using modified International Working Group (IWG) criteria (2007). Analysis population consisted of Per Protocol Set(PPS) (all participants in the Full Analysis Set(FAS) defined as all participants who received at least 1 dose of YM155), who also met the following: Histologically-confirmed CD20-positive, primary/transformed diffuse large B-cell lymphoma (DLBCL) &/or grade 3 follicular lymphoma(FL). Relapsed/transformed low grade non-Hodgkin's Lymphoma(NHL) to a DLBCL & documented at least a PR for 3 months prior to progression, following receipt of last dose systemic chemotherapy/autologous stem cell transplant(ASCT). No known central nervous system(CNS) involvement, history of other malignancy or disease free for at least 5 years (with exception of non-invasive cancers), no major protocol deviations/use prohibited concomitant medications. 9999=not available, n=number of participants.

End point type	Primary

End point timeframe:

After the last non-progressing participant received 8 cycles of treatment or discontinued the treatment (by data cut off for primary analysis of 05 March 2013)

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: Not applicable, descriptive summary statistics provided for the primary endpoint.

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 90%)				
All participants (n=34)	50 (34.9 to 65.1)			
Age ≤ 60 (n = 11)	63.6 (35 to 86.5)			
Age > 60 (n = 23)	43.5 (25.8 to 62.5)			
Sex Male (n = 22)	54.5 (35.3 to 72.9)			
Sex Female (n = 12)	41.7 (18.1 to 68.5)			
Race White (n = 33)	48.5 (33.3 to 63.9)			
Race Black or African American (n=1)	100 (5 to 100)			

ECOG performance Grade 0 (n = 20)	55 (34.7 to 74.1)			
ECOG performance Grade 1 (n = 14)	42.9 (20.6 to 67.5)			
Diffuse Large B-Cell Lymphoma (n = 33)	51.5 (36.1 to 66.7)			
Follicular Lymphoma (Grade 3) (n = 1)	9999 (9999 to 9999)			
Lymphoma Prognostic Index Low (n = 5)	40 (7.6 to 81.1)			
Lymphoma Prognostic Index Intermediate (n = 21)	47.6 (28.6 to 67.2)			
Lymphoma Prognostic Index High (n = 8)	62.5 (28.9 to 88.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed Complete Remission Rate (CR)

End point title	Confirmed Complete Remission Rate (CR)

End point description:

CR rate was based on percentage of participants with CR. Investigator's assessment of tumor response was based on imaging scans that were performed 6-8 weeks after the response was first detected per IWG revised Responses Criteria for malignant lymphoma (2007). Best objective response was derived on time point response reported by the investigator. Analysis population consisted of the PPS.

End point type	Secondary

End point timeframe:

After the last non-progressing participant received 8 cycles of treatment or discontinued the treatment (by data cut off for primary analysis of 05 March 2013)

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 90%)	20.6 (10.1 to 35.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed Partial Remission Rate (PR)

End point title	Confirmed Partial Remission Rate (PR)

End point description:

Confirmed PR was based on percentage of participants with PR. Investigator's assessment of tumor response was based on imaging scans that were performed 6-8 weeks after the response was first

detected per IWG revised Responses Criteria for malignant lymphoma (2007). Best objective response was derived on time point response reported by the investigator. Analysis population consisted of the PPS.

End point type	Secondary

End point timeframe:

After the last non-progressing participant received 8 cycles of treatment or discontinued the treatment (by data cut off for primary analysis of 05 March 2013)

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 90%)	29.4 (16.9 to 44.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Response (TTR)

End point title	Time To Response (TTR)

End point description:

Time to response was based on the investigator’s assessment of tumor response in participants with confirmed CR or confirmed PR and calculated using Kaplan-Meier estimates and defined as the time from the first dose of study drug until the first documentation of response (CR or PR). Analysis population consisted of the PPS. N is the number of responders/participants/patients with confirmed CR or confirmed PR.

End point type	Secondary

End point timeframe:

From first dose of study drug to data cut off for primary analysis of 05 March 2013

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: days				
median (confidence interval 95%)	56 (52 to 57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Duration of response was defined as the time from the first documentation of response (CR or PR) until objective tumor/disease progression. N is the number of responders/participants/patients with confirmed CR or confirmed PR. Analysis population consisted of the PPS. The median duration of response could not be estimated (calculated using Kaplan-Meier estimates) because the value of the smallest observed survival function was > 0.5. At the time of the analysis, the upper limit of the confidence could not be estimated. 9999=not available

End point type	Secondary

End point timeframe:

From first dose of study drug to data cut off for primary analysis of 05 March 2013

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: days				
median (confidence interval 95%)	9999 (176 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

Clinical benefit rate (CR + PR + stable disease) defined as percentage of participants with confirmed CR, confirmed PR and stable disease was based on the investigator's assessment of tumor response in all participants. Analysis population consisted of the PPS. Stable disease (SD) defined per IWG criteria (2007) as the following: A subject is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease. Typically fluoro-deoxy-glucose (FDG)-avid lymphomas: the Positron Emission Tomography (PET) should be positive at prior sites of disease with no new areas of involvement on the post-treatment Computed Tomography (CT) or PET. Variably FDG-avid lymphomas/FDG-avidity unknown: for subjects without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

End point type	Secondary

End point timeframe:

After the last non-progressing participant received 8 cycles of treatment or discontinued the treatment (by data cut off for primary analysis of 05 March 2013)

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: percentage of participants				
number (confidence interval 90%)	82.4 (68.1 to 92)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was defined as the time from the first dose of study drug until objective tumor progression or death and was based on the investigator's assessment of tumor response in all participants and calculated using Kaplan-Meier estimates. Analysis population consisted of the PPS. Disease progression includes progression based radiological outcome and clinical signs and symptoms per IWG criteria. At the time of the analysis, the upper limit of the confidence could not be estimated. 9999=not available

End point type	Secondary

End point timeframe:

From first dose of study drug to data cut off for primary analysis of 05 March 2013

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: days				
median (confidence interval 95%)	537 (154 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time from the first dose of study drug until death. Analysis population consisted of the PPS. Participants without death date were censored. The median OS could not be estimated (calculated using Kaplan-Meier estimates) because the value of the smallest observed survival function was > 0.5. Median survivor time could not be estimated due to the value of the smallest observed survival function > 0.5. Median survivor time could not be estimated due to the value of the smallest observed survival function > 0.5. At the time of the analysis, the upper limit of the confidence could not be estimated. 9999=not available

End point type	Secondary

End point timeframe:

From first dose of study drug to data cut off for primary analysis of 05 March 2013

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	34			
Units: days				
median (confidence interval 95%)	9999 (483 to 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs)

End point title	Number of participants with adverse events (AEs)

End point description:

Analysis population consisted of the Safety Analysis Set (SAF) population. The SAF was defined as all patients who received at least 1 dose of study regimen (rituximab or YM155). An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug or study regimen and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug or study regimen, whether or not related to the study drug or study regimen. Treatment-emergent adverse event (TEAE) was defined as an AE starting after first administration of the study drug up to the End of Treatment Visit (ETV).

End point type	Secondary

End point timeframe:

From first dose of study drug to data cut off for primary analysis of 05 March 2013

End point values	YM155 plus rituximab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Participants				
Any TEAE	38			
Drug-related TEAEs	29			
Deaths	4			
Serious TEAEs	26			
Drug-related Serious TEAEs	12			
TEAEs Leading to Discontinuation	10			
Drug-related TEAEs Leading to Discontinuation	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to data cut off for primary analysis of 05 March 2013.

Adverse event reporting additional description:

Treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) starting after first administration of the study drug up to the End of Treatment Visit (ETV).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	YM155 plus rituximab

Reporting group description:

Participants were administered YM155 and rituximab during 14-day cycles. Rituximab (375 mg/m^2) was administered weekly on days 1 and 8 during cycles 1 to 4, repeated every 10 cycles (i.e., cycles 11-14, 21-24, etc.). YM155 (5 mg/m^2 per day iv) was administered by continuous infusion for 168 hours via a central line, port or peripherally-inserted central catheter (PICC) from days 1 to 8 of each cycle.

Serious adverse events	YM155 plus rituximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 41 (63.41%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Jugular vein thrombosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena caval occlusion			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Catheter related complication			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter thrombosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Disease progression				
subjects affected / exposed	3 / 41 (7.32%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Hyperthermia				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion site extravasation				
subjects affected / exposed	3 / 41 (7.32%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Infusion site necrosis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	3 / 41 (7.32%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

Pulmonary embolism			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Rash generalised			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin necrosis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal failure acute			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Catheter related infection			

subjects affected / exposed	5 / 41 (12.20%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Central line infection				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective thrombosis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lemierre syndrome				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mediastinitis				
subjects affected / exposed	1 / 41 (2.44%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				

subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	YM155 plus rituximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 41 (82.93%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	8		
Chills			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	13 / 41 (31.71%)		
occurrences (all)	20		
Oedema peripheral			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	13 / 41 (31.71%)		
occurrences (all)	34		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 41 (29.27%)		
occurrences (all)	16		
Dyspnoea			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 41 (12.20%)		
occurrences (all)	5		
Insomnia			

subjects affected / exposed occurrences (all)	7 / 41 (17.07%) 8		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 4 8 / 41 (19.51%) 12 3 / 41 (7.32%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 10 / 41 (24.39%) 14 9 / 41 (21.95%) 72 6 / 41 (14.63%) 9		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 4		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 5 / 41 (12.20%) 6 5 / 41 (12.20%) 7		

Diarrhoea subjects affected / exposed occurrences (all)	10 / 41 (24.39%) 16		
Nausea subjects affected / exposed occurrences (all)	10 / 41 (24.39%) 14		
Stomatitis subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 5		
Vomiting subjects affected / exposed occurrences (all)	9 / 41 (21.95%) 19		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 8		
Arthralgia subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 6		
Musculoskeletal pain subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Muscle spasms subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		
Pain in extremity subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 7		
Infections and infestations Oral candidiasis subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4		

Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 4 / 41 (9.76%) 5 6 / 41 (14.63%) 8		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	 3 / 41 (7.32%) 3 5 / 41 (12.20%) 6 3 / 41 (7.32%) 4 3 / 41 (7.32%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2009	Remove the collection of tumor biopsy slides and bone marrow slides as inclusion criteria. Remove the requirement to collect tumor biopsy slides for biomarker analysis. Update the Events Always Considered to be Serious List. Remove the statement on the protocol cover page regarding legal representation of sponsor as stipulated under Directive 2001/20/EC of the European Parliament and of the Council.
21 January 2010	Clarify that registration was to occur as close as possible to day 1 of cycle 1. Update the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version. Update the Overall Response Rate to ORR. Update the primary variable definition. Update the safety variable in the synopsis to match the safety variable in the main protocol. Update the CR and PR variable definition. Add safety analysis after the 10th patient completed 1 cycle of YM155 plus rituximab treatment. Update inclusion criteria. Remove the acceptability of a legally authorized representative consenting on a patient's behalf. Update the inclusion/exclusion criteria. Add cycle 1 day 2 visit and a physical exam in the cycle 1 day 4 visit. Update the test drug storage condition. Highlight that generic rituximab could not be administered to study patients. Update the drug destruction and drug return requirement. Update the medical history and baseline condition definition. Update language regarding consistency in radiological review of scans and that diagnostic quality computed tomography (CT) scans were required. Update the lab assessment to include hepatitis tests. Update language to clarify that other staining methods such as, but not limited to, immunohistochemistry (IHC) could be conducted. Clarification on AE assessment and documentation. Update blood collection volumes. Update procedure in case of pregnancy. Update the statistical analysis. Appendices updated.
04 May 2010	Revise inclusion and exclusion criteria. Update the protocol introduction to include information that was then available in the Investigator's Brochure and clinical database for YM155. Allow for investigator discretion in lowering of the YM155 dose. Clarify the retreatment criterion regarding toxicities. Clarify AE descriptions for rituximab. Provide guidance for destroying or returning study drug. Provide guidance for administering growth factors. Revise the frequency of post-treatment imaging. Clarify the type of imaging used when contrast CT was contraindicated. Clarify how YM155 dose interruptions were to be handled Clarify procedures for administering rituximab and YM155. Clarify where medical history and baseline conditions were recorded on the case report form (CRF). Allow for dosing of rituximab and YM155 at the same time on day 8. Clarify statistical methodology.
12 July 2010	Clarify inclusion criterion regarding prior chemotherapy, prior malignancies and definition of relapse. Clarify biomarker testing. Clarify serious adverse event (SAE) reporting period.
07 July 2011	Delete all reference to Canada. Clarify accepted scans prior to informed consent. Update study timelines. Clarify inclusion criteria 5, 9, and 10. Add a window to the screening period CT and FDG-PET scans. Update statistical methods. Clarify what scans needed to be obtained after a PR/CR. Clarify YM155 dosing per patient's weight. Delete vital signs and electrocardiogram (ECG) on cycle 1, days 2 and 6. Add a window to the follow-up CT and magnetic resonance imaging (MRI) scans. Clarify the SAE capturing of agranulocytosis (myelosuppression). Add Drug-Induced Liver Injury (DILI) information. Clarify the minimum of days in each cycle. Add a window to allow scans obtained (±) 3 days at the 12-week follow-up visit.

23 February 2012	Incorporate updated safety language. Update the planned study period. Decrease the sample size. The sample size was reduced from 60 to 40 patients based on the efficacy and safety data from interim analyses, which suggested that findings from 40 patients in this proof-of-concept study would be sufficient to plan subsequent studies. Delete specific assessments due to lack of safety alert signals. Decrease the estimated total amount of blood drawn based on fewer planned laboratory assessments. Update the imaging and statistical portion of the protocol to change the assessment of the primary endpoint to the Investigator
30 October 2012	Update the projected last patient out date. Clarify the criteria used for ORR. Remove the timeframe for inclusion criteria 1 (aged 18 years or older), as it was not applicable. Clarify patient assessment regarding life expectancy was based on investigator's judgment. Clarify adequate method of birth control. Clarify exclusion criteria 8. Clarify prohibited medications or therapies while on study. Update the 1) number of patients in the PPS and the number of observed ORR at final analysis, 2) number of non-progressing patients in the PPS, and 3) power and the observed ORR at final analysis, all to correspond with the updated PPS definition. Clarify when diagnostic CT and FDG-PET scans were performed. Clarify when patients were contacted during the survival follow-up period. Delete Appendix 10 (Events Always Considered to be Serious), as the listing was not mandated by regulations. Clarify timing of study termination if the study had to be closed for any reason. Clarify the version of CTCAE being used for the study. Include further instructions to Investigators for reporting protocol deviations to the Sponsor. Clarify best objective response in the event of a CR to a PR.
12 September 2013	Clarify the obligations for reporting SAEs. Ensure that the principal investigator's protocol acknowledgement adhered to country-specific regulations, as applicable. Update the current study period. Clarify the end of trial in the protocol. Update the number or timing of assessment to either clarify the data collection endpoint or to reflect standard of care. Include a systematic process for identifying and summarizing protocol deviations.

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.

The primary analysis is considered final and no end of study report will be completed. The 7 ongoing participants at the time of the data cutoff are now completed.

Notes: