Clinical trial results:
Phase III multicentre open-label randomised study of ICE plus Rituximab (R-ICE) versus DHAP plus Rituximab (R-DHAP) in previously treated patients with CD 20 positive diffuse large B-cell lymphoma, eligible for transplantation followed by randomised maintenance treatment with Rituximab

Summary

EudraCT number	2004-002103-32
Trial protocol	IE
Global end of trial date	16 January 2014

Results information

Result version number	v1 (current)
This version publication date	12 May 2018
First version publication date	12 May 2018
Summary attachment (see zip file)	CORAL_SUMMARY OF RESULTS (CORAL_Clinical Study Report.pdf)

Trial information

Trial identification

Sponsor protocol code	50-03B

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	LYSARC
Sponsor organisation address	Centre Hospitalier Lyon-Sud - Secteur Sainte Eugénie - Pavillon 6D, PIERRE-BENITE, France, 69495
Public contact	Julie Assémat, LYSARC, 33 0472669333, julie.assemat@lysarc.org
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 October 2008
Global end of trial reached?	Yes
Global end of trial date	16 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the induction therapy is to evaluate the efficacy and safety of ICE plus Rituximab (R-ICE) in comparison with DHAP plus Rituximab (R-DHAP) in previously treated patients with CD20 positive diffuse large B cell lymphoma eligibale for autologous transplantation
The objective of the maintenance therapy is to evaluate the efficacy and safety of Rituximab maintenance therapy after transplantation

Protection of trial subjects:

If a patient does not respond, relapses or has progressive disease, every center was free to initiate further treatment according to local guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 July 2003
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	Ireland: 4
Country: Number of subjects enrolled	Australia: 42
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	France: 128
Country: Number of subjects enrolled	Germany: 111
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	New Zealand: 16
Country: Number of subjects enrolled	Switzerland: 24
Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	United Kingdom: 50
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	477
EEA total number of subjects	373

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)	460
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period from January 2003 until mid/end 2008

Pre-assignment

Screening details:

- Patient with histologically proven, CD 20+ diffuse large B cell lymphoma in 1st relapse afterCR, less than PR or partial response to first line treatment
- Aged from 18 to 65 years, inclusive
- Eligible for transplant
- Previously treated with chemotherapy regimen containing anthracyclines with or without rituximab
- ECOG performance status

Period 1

Period 1 title	Induction
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R-ICE

Arm description: -

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

Dosage and administration details:

375mg/m2

Arm title	R-DHAP

Arm description: -

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

Dosage and administration details:

375mg/m2

Number of subjects in period 1	R-ICE	R-DHAP
Started	243	234
Completed	205	196
Not completed	38	38
Consent withdrawn by subject	2	2
death	4	6
unknown	2	1
Adverse event, non-fatal	7	4
Lack of efficacy	20	24
Protocol deviation	3	1

Period 2	
Period 2 title	Consolidation
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	BEAM + ASCT (R-ICE)
Arm description: Consolidation treatment after R-ICE	
Arm type	consolidation
No investigational medicinal product assigned in this arm	
Arm title	BEAM + ASCT (R-DHAP)
Arm description: Consolidation treatment after R-DHAP	
Arm type	consolidation
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	BEAM + ASCT (R-ICE)	BEAM + ASCT (R-DHAP)
Started	205	196
Completed	116	126
Not completed	89	70
Consent withdrawn by subject	1	2
death	3	2
unknown	10	11
Adverse event, non-fatal	-	6

Lack of efficacy	74	49
Protocol deviation	1	-

Period 3	
Period 3 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Observation

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Rituximab

Arm description: -

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

Dosage and administration details:
375mg/m2

Number of subjects in period 3	Observation	Rituximab
Started	120	122
Completed	41	30
Not completed	81	92
Adverse event, serious fatal	1	3
Consent withdrawn by subject	3	6
death	39	42
Adverse event, non-fatal	-	3
Transferred to other arm/group	-	2
Lost to follow-up	-	1
Lack of efficacy	38	35
Joined	2	0

Transferred in from other group/arm	2	-

Baseline characteristics

Reporting groups	
Reporting group title	R-ICE
Reporting group description: -	
Reporting group title	R-DHAP
Reporting group description: -	

Reporting group values	R-ICE	R-DHAP	Total
Number of subjects	243	234	477
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
R-ICE (N=242): mean = 50.7 median = 54.0 min = 19; max = 65 R-DHAP (N=234) mean = 52.3 median = 55.0 min = 19; max = 65			
Units: years			
median	54	55	
full range (min-max)	19 to 65	19 to 65	-
Gender categorical Units: Subjects			
Female	87	87	174
Male	156	147	303

Subject analysis sets	
Subject analysis set title	Induction Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: (following the intent-to-treat principle) refers to all randomized patients regardless they have received study treatment or not: 477 patients analyzed according the therapy they were randomized to receive (243 in R-ICE arm and 234 in RDHAP arm).	
Subject analysis set title	Induction Intent To Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

refers to patients receiving at least one injection of study treatment, regardless the quantity injected: 469 patients analyzed according the therapy they were randomized to receive (239 in R-ICE arm and 230 in RDHAP arm).

Subject analysis set title	Induction Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

refers to patients receiving at least one injection of study treatment: 469 patients analyzed according the therapy they actually received (239 in R-ICE arm and 230 in R-DHAP arm).

Subject analysis set title	Maintenance Intent To Treat Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

refers to all patients formally randomized in the 2nd part of the study: 242 patients analyzed according the therapy they were randomized to receive (122 in rituximab arm and 120 in observation arm).

Subject analysis set title	Maintenance Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

refers to all patients formally randomized in the 2nd part of the study and have received at least one dose of rituximab or have only been observed, and have at least one maintenance follow-up assessment: 235 patients analyzed according the therapy they actually received, i.e. patient will be included in rituximab arm if he/she had received at least one dose of rituximab during any maintenance visit otherwise, he/she will be included in observation arm (thus, 116 in rituximab arm and 119 in observation arm).

Reporting group values	Induction Full Analysis Set	Induction Intent To Treat Population	Induction Safety population
Number of subjects	477	469	469
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
R-ICE (N=242): mean = 50.7 median = 54.0 min = 19; max = 65 R-DHAP (N=234) mean = 52.3 median = 55.0 min = 19; max = 65			
Units: years median full range (min-max)	 54 19 to 65		

Gender categorical Units: Subjects			
Female Male			

Reporting group values	Maintenance Intent To Treat Population	Maintenance Safety Population	
Number of subjects	242	235	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
R-ICE (N=242): mean = 50.7 median = 54.0 min = 19; max = 65 R-DHAP (N=234) mean = 52.3 median = 55.0 min = 19; max = 65			
Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	R-ICE
Reporting group description: -	
Reporting group title	R-DHAP
Reporting group description: -	
Reporting group title	BEAM + ASCT (R-ICE)
Reporting group description: Consolidation treatment after R-ICE	
Reporting group title	BEAM + ASCT (R-DHAP)
Reporting group description: Consolidation treatment after R-DHAP	
Reporting group title	Observation
Reporting group description: -	
Reporting group title	Rituximab
Reporting group description: -	
Subject analysis set title	Induction Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: (following the intent-to-treat principle) refers to all randomized patients regardless they have received study treatment or not: 477 patients analyzed according the therapy they were randomized to receive (243 in R-ICE arm and 234 in RDHAP arm).	
Subject analysis set title	Induction Intent To Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: refers to patients receiving at least one injection of study treatment, regardless the quantity injected: 469 patients analyzed according the therapy they were randomized to receive (239 in R-ICE arm and 230 in RDHAP arm).	
Subject analysis set title	Induction Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: refers to patients receiving at least one injection of study treatment: 469 patients analyzed according the therapy they actually received (239 in R-ICE arm and 230 in R-DHAP arm).	
Subject analysis set title	Maintenance Intent To Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: refers to all patients formally randomized in the 2nd part of the study: 242 patients analyzed according the therapy they were randomized to receive (122 in rituximab arm and 120 in observation arm).	
Subject analysis set title	Maintenance Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: refers to all patients formally randomized in the 2nd part of the study and have received at least one dose of rituximab or have only been observed, and have at least one maintenance follow-up assessment: 235 patients analyzed according the therapy they actually received, i.e. patient will be included in rituximab arm if he/she had received at least one dose of rituximab during any maintenance visit otherwise, he/she will be included in observation arm (thus, 116 in rituximab arm and 119 in observation arm).	

Primary: Mobilization Adjusted Response Rate after induction chemotherapy

End point title	Mobilization Adjusted Response Rate after induction chemotherapy

End point description:

MARR = overall response rate (ORR) (CR/CRu/PR) adjusted with successful mobilization at the end of 2 and/or 3 cycles of induction chemotherapy treatment before high-dose chemotherapy and autologous transplantation

Responses are defined, according to Cheson et al (6), response after 3 cycles of treatment will be evaluated by an external expert committee after recommendation from the steering committee (CR, CRu, PR, SD, PD and relpased disease for patients in CR or CRu).

End point type	Primary

End point timeframe:

It will be a composite endpoint including response rate and success of mobilization of stem cells. Response rate after 3 cycles of chemotherapy and at the end of treatment.

End point values	R-ICE	R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239[1]	230[2]		
Units: percent				
number (confidence interval 95%)	51.5 (44.9 to 58.0)	56.5 (49.8 to 63.0)		

Notes:

[1] - Induction ITT set
R-ICE arm
[2] - Induction ITT arm
R-CHOP arm

Statistical analyses

Statistical analysis title	Primary criterion - Induction
Comparison groups	R-DHAP v R-ICE
Number of subjects included in analysis	469
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.272
Method	Chi-squared
Parameter estimate	OR rates difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.1
upper limit	4

Primary: Event free survival after transplant

End point title	Event free survival after transplant

End point description:

Events are defined as follows:

- Progression of the lymphoma during or after treatment for patients who achieved a response qualified as stable disease or PR,
- Relapse for CR and CRu patients,
- Institution of a new treatment for the lymphoma
- Death from any cause, without progression.

Event-Free Survival (EFS) is measured from date of 2nd randomization to date of first event on the Maintenance ITT population.

End point type	Primary

End point timeframe:

EFS at 2-years in months

End point values	Observation	Rituximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	122		
Units: percent				
number (confidence interval 95%)	59.3 (49.8 to 67.5)	59.2 (49.7 to 67.5)		

Statistical analyses

Statistical analysis title	Primary criterion - Maintenance
Comparison groups	Observation v Rituximab
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.7435
Method	Logrank

Notes:

[3] - The event free survival post transplant will be analyzed using the stratified log rank test.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) occurring during the treatment period and until 30 days after the end of the last cycle of treatment or last dose of Rituximab will be recorded on the toxicity forms

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	R-ICE
Reporting group description: -	
Reporting group title	R-DHAP

Reporting group description: -

Serious adverse events	R-ICE	R-DHAP	
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 239 (27.62%)	84 / 234 (35.90%)	
number of deaths (all causes)	126	15	
number of deaths resulting from adverse events	9	15	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma	Additional description: All these neoplasms are reported in the table below		
subjects affected / exposed	4 / 239 (1.67%)	3 / 234 (1.28%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	2 / 2	1 / 1	
Vascular disorders			
Thrombosis	Additional description: All vascular disorders are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hepatectomy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

pyrexia	Additional description: All general disorders are reported in the table below		
subjects affected / exposed	5 / 239 (2.09%)	6 / 234 (2.56%)	
occurrences causally related to treatment / all	0 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
social stay hospitalisation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
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			
respiratory failure	Additional description: All respiratory, thoracic and mediastinal disorders are reported in the table below		
subjects affected / exposed	6 / 239 (2.51%)	5 / 234 (2.14%)	
occurrences causally related to treatment / all	2 / 6	5 / 5	
deaths causally related to treatment / all	2 / 2	5 / 5	
Psychiatric disorders			
Depression	Additional description: All psychiatric disorders are reported in the table below		
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma	Additional description: All these complications are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

cardiac failure	Additional description: All cardiac disorders are reported in the able below		
subjects affected / exposed	6 / 239 (2.51%)	5 / 234 (2.14%)	
occurrences causally related to treatment / all	2 / 6	1 / 5	
deaths causally related to treatment / all	2 / 2	1 / 1	
Nervous system disorders			
Cerebrovascular accident	Additional description: All nervous system disorders are reported in the table below		
subjects affected / exposed	4 / 239 (1.67%)	13 / 234 (5.56%)	
occurrences causally related to treatment / all	0 / 4	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia	Additional description: All blood and lymphatic system disorders are reported in the table below		
subjects affected / exposed	11 / 239 (4.60%)	16 / 234 (6.84%)	
occurrences causally related to treatment / all	0 / 11	2 / 16	
deaths causally related to treatment / all	0 / 0	2 / 2	
Ear and labyrinth disorders			
deafness	Additional description: All ear and labyrinth disorders are reported in the table below		
subjects affected / exposed	1 / 239 (0.42%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder	Additional description: All gastrointestinal disorders are reported in the table below		
subjects affected / exposed	10 / 239 (4.18%)	19 / 234 (8.12%)	
occurrences causally related to treatment / all	0 / 10	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
hepatitis	Additional description: All hepatobiliary disorders are reported in the table below		
subjects affected / exposed	3 / 239 (1.26%)	0 / 234 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin reaction			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure	Additional description: All renal and urinary disorders are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	12 / 234 (5.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain	Additional description: All these disorders are reported in the table below		
subjects affected / exposed	1 / 239 (0.42%)	2 / 234 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Neutropenic sepsis	Additional description: All SAE related to infections and infestations are reported in the table below		
subjects affected / exposed	46 / 239 (19.25%)	55 / 234 (23.50%)	
occurrences causally related to treatment / all	3 / 46	4 / 55	
deaths causally related to treatment / all	3 / 3	4 / 4	
Metabolism and nutrition disorders			
Dehydration	Additional description: All metabolism and nutrition disorders are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	6 / 234 (2.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.7 %

Non-serious adverse events	R-ICE	R-DHAP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	154 / 239 (64.44%)	172 / 234 (73.50%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour lysis syndrome	Additional description: All these neoplasms are reported in the table below		
subjects affected / exposed	4 / 239 (1.67%)	7 / 234 (2.99%)	
occurrences (all)	4	7	
Vascular disorders			
Thrombosis	Additional description: All vascular disorders are reported in the table below		
subjects affected / exposed	6 / 239 (2.51%)	7 / 234 (2.99%)	
occurrences (all)	6	7	
Surgical and medical procedures			

Hepatectomy			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia	Additional description: All general disorders are reported in the table below		
subjects affected / exposed	40 / 239 (16.74%)	51 / 234 (21.79%)	
occurrences (all)	40	51	
Immune system disorders			
Drug hypersensitivity	Additional description: All immune system disorders are reported in the table below		
subjects affected / exposed	4 / 239 (1.67%)	5 / 234 (2.14%)	
occurrences (all)	4	5	
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	0 / 239 (0.00%)	1 / 234 (0.43%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	Additional description: All respiratory, thoracic and mediastinal disorders are reported in the table below		
subjects affected / exposed	10 / 239 (4.18%)	11 / 234 (4.70%)	
occurrences (all)	10	11	
Psychiatric disorders			
depression	Additional description: All psychiatric disorders are reported in the table below		
subjects affected / exposed	1 / 239 (0.42%)	3 / 234 (1.28%)	
occurrences (all)	1	3	
Investigations			
Blood creatinine increased	Additional description: All investigations are reported in the table below		
subjects affected / exposed	12 / 239 (5.02%)	17 / 234 (7.26%)	
occurrences (all)	12	17	
Injury, poisoning and procedural complications			
drug toxicity	Additional description: All these complications are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	2 / 234 (0.85%)	
occurrences (all)	2	2	
Cardiac disorders			
cadiac failure	Additional description: All cardiac disorders are reported in the table below		
subjects affected / exposed	7 / 239 (2.93%)	6 / 234 (2.56%)	
occurrences (all)	7	6	
Nervous system disorders			

Cerebrovascular accident	Additional description: All nervous system disorders are reported in the table below		
subjects affected / exposed	7 / 239 (2.93%)	19 / 234 (8.12%)	
occurrences (all)	7	19	
Blood and lymphatic system disorders			
neutropenia	Additional description: All blood and lymphatic disorders are reported in the table below		
subjects affected / exposed	64 / 239 (26.78%)	116 / 234 (49.57%)	
occurrences (all)	64	116	
Ear and labyrinth disorders			
deafness	Additional description: All ear and labyrinth disorders are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	4 / 234 (1.71%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Vomiting	Additional description: All GI disorders are reported in the table below		
subjects affected / exposed	33 / 239 (13.81%)	65 / 234 (27.78%)	
occurrences (all)	33	65	
Hepatobiliary disorders			
hepatitis	Additional description: All hepatobiliary disorders are reported in the table below		
subjects affected / exposed	3 / 239 (1.26%)	5 / 234 (2.14%)	
occurrences (all)	3	5	
Skin and subcutaneous tissue disorders			
Skin reaction	Additional description: All skin and subcutaneous tissue disorders are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	1 / 234 (0.43%)	
occurrences (all)	2	1	
Renal and urinary disorders			
renal failure acute	Additional description: All renal and urinary disorders are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	21 / 234 (8.97%)	
occurrences (all)	2	21	
Musculoskeletal and connective tissue disorders			
Bone pain	Additional description: All musculoskeletal and connective tissue disorders are reported in the table below		
subjects affected / exposed	2 / 239 (0.84%)	4 / 234 (1.71%)	
occurrences (all)	2	4	
Infections and infestations			
Infection	Additional description: All infections and infestations are reported in the table below		
subjects affected / exposed	135 / 239 (56.49%)	166 / 234 (70.94%)	
occurrences (all)	135	166	
Metabolism and nutrition disorders			

hypokaliemia	Additional description: All metabolism and nutrition disorders are reported in the table below		
subjects affected / exposed	11 / 239 (4.60%)	40 / 234 (17.09%)	
occurrences (all)	11	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 July 2007	La première analyse de sécurité et l'analyse intermédiaire réalisées dans le cadre de l'étude citée en référence ont montré que le nombre de randomisations prévues dans la deuxième partie de l'étude ne serait pas atteint. Le taux de sorti d'essai avant la deuxième randomisation atteignant 50 %. L'augmentation du recrutement à 480 patients est nécessaire pour atteindre l'objectif de la deuxième partie de l'étude. En second lieu, l'amendement prend en compte le changement du Résumé des Caractéristiques du Produit du Mabthera mis à jour au 12 janvier 2007.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported