Clinical trial results:
Etude multicentrique de phase III randomisée ouverte testant l’efficacité du gemtuzumab ozogamycin (MYLOTARG®) en association avec la chimiothérapie intensive chez les patients de 18 à 60 ans atteints de leucémie aiguë myéloblastique (LAM) avec cytogénétique intermédiaire.

Summary

EudraCT number	2007-001209-64
Trial protocol	FR
Global end of trial date	26 September 2016

Results information

Result version number	v1 (current)
This version publication date	17 March 2019
First version publication date	17 March 2019

Trial information

Trial identification

Sponsor protocol code	BRD 06/10-I

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00860639
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU Nantes
Sponsor organisation address	5 allée de l'Ile Gloriette, Nantes, France, 44093
Public contact	Pr MOREAU, CHU Nantes, philippe.moreau@chu-nantes.fr
Scientific contact	Pr MOREAU, CHU Nantes, philippe.moreau@chu-nantes.fr

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	09 July 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Démontrer la supériorité de l'addition de gemtuzumab ozogamycin (Mylotarg®) à la chimiothérapie d'induction et de consolidation vs chimiothérapie seule en terme de survie sans évènement (event free survival : EFS) pour les patients âgés de 18 à 60 ans présentant une LAM avec cytogénétique intermédiaire non éligibles pour une allogreffe standard.

Protection of trial subjects:

Very close follow-up of the patients with biological analysis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2007
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	France: 327
Worldwide total number of subjects	327
EEA total number of subjects	327

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)	327
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Intermediate acute leukaemia

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Induction course :
- Daunorubicin : 60 mg / m²/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m²/ day continuous infusion, D1, D2, D3, D4, D5, D6, D7
- Mylotarg® : 6 mg/m² via slow IV route for 2 hours on D4
- Premedication is required consisting of paracetamol 1g associated with an antihistamine : Dexchlorpheniramine 5 mg (Polaramine®) one hour before starting Mylotarg®
- Monitoring during infusion should include blood pressure and heart beat readings every 15 minutes for the first hour and subsequently every 30 minutes for 3 hours.

Consolidation course :
- Mitoxantrone : 12 mg / m2/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m2 x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5
- Mylotarg® : 6 mg/ m2 via slow IV route for 2 hours on D4

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

Dosage and administration details:

6 mg/m² via slow IV route for 2 hours on D4

Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg / m²/ day slow IV for 15 minutes at D1, D2, D3

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Induction course : 200 mg / m²/ day, continuous infusion at D1, D2, D3, D4, D5, D6, D7
- Consolidation course : 1 g / m² x 2 / day via IV infusion for 3 hours at D1, D2, D3, D4, D5

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg / m2/ day slow IV for 15 minutes at D1, D2

Arm title	Arm B

Arm description:

Induction course :
- Daunorubicin : 60 mg / m²/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m²/ day, continuous infusion, D1, D2, D3, D4, D5, D6, D7

Consolidation course :
- Mitoxantrone : 12 mg / m2/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m2 x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5

Arm type	Active comparator
Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg / m²/ day slow IV for 15 minutes at D1, D2, D3

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Induction course : 200 mg / m²/ day, continuous infusion at D1, D2, D3, D4, D5, D6, D7
- Consolidation course : 1 g / m² x 2 / day via IV infusion for 3 hours at D1, D2, D3, D4, D5

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg / m2/ day slow IV for 15 minutes at D1, D2

Number of subjects in period 1[1]	Arm A	Arm B
Started	119	119
Completed	55	57
Not completed	64	62
Premature discontinuation	64	62

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The difference is due to the fact that the study has 2 periods.

Period 2

Period 2 title	Second step
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Arm title	Arm B

Arm description:

Induction course :
- Daunorubicin : 60 mg / m²/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m²/ day, continuous infusion, D1, D2, D3, D4, D5, D6, D7

Consolidation course :
- Mitoxantrone : 12 mg / m2/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m2 x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5

Arm type	Active comparator
Investigational medicinal product name	Daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg / m²/ day slow IV for 15 minutes at D1, D2, D3

Investigational medicinal product name	Mitoxantrone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg / m2/ day slow IV for 15 minutes at D1, D2

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

- Induction course : 200 mg / m²/ day, continuous infusion at D1, D2, D3, D4, D5, D6, D7
- Consolidation course : 1 g / m² x 2 / day via IV infusion for 3 hours at D1, D2, D3, D4, D5

Number of subjects in period 2[2]	Arm B
Started	73
Completed	73

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The difference is due to the fact that the study has 2 periods.

Baseline characteristics

Reporting groups	
Reporting group title	First step

Reporting group description: -

Reporting group values	First step	Total	
Number of subjects	238	238	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	238	238	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	108	108	
Male	130	130	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Induction course :
- Daunorubicin : 60 mg / m²/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m²/ day continuous infusion, D1, D2, D3, D4, D5, D6, D7
- Mylotarg® : 6 mg/m² via slow IV route for 2 hours on D4
- Premedication is required consisting of paracetamol 1g associated with an antihistamine : Dexchlorpheniramine 5 mg (Polaramine®) one hour before starting Mylotarg®
- Monitoring during infusion should include blood pressure and heart beat readings every 15 minutes for the first hour and subsequently every 30 minutes for 3 hours.

Consolidation course :
- Mitoxantrone : 12 mg / m2/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m2 x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5
- Mylotarg® : 6 mg/ m2 via slow IV route for 2 hours on D4

Reporting group title	Arm B

Reporting group description:

Induction course :
- Daunorubicin : 60 mg / m²/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m²/ day, continuous infusion, D1, D2, D3, D4, D5, D6, D7

Consolidation course :
- Mitoxantrone : 12 mg / m2/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m2 x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5

Reporting group title	Arm B

Reporting group description:

Induction course :
- Daunorubicin : 60 mg / m²/ day, slow IV for 15 minutes, D1, D2, D3
- Cytarabine : 200 mg / m²/ day, continuous infusion, D1, D2, D3, D4, D5, D6, D7

Consolidation course :
- Mitoxantrone : 12 mg / m2/ day, slow IV for 15 minutes, D1, D2
- Cytarabine : 1 g / m2 x 2 / day (every 12 hours) via IV infusion for 3 hours, D1, D2, D3, D4, D5

Primary: Event-free survival

End point title	Event-free survival[1]

End point description:

Demonstrate the superiority of adding gemtuzumab ozogamycin (Mylotarg®) to induction and consolidation chemotherapy vs chemotherapy alone in terms of event-free survival (EFS) for patients from 18 to 60 years of age presenting AML with intermediate cytogenetics not eligible for a standard allograft.

End point type	Primary

End point timeframe:

3 years

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: Due to the premature discontinuation of the study, il was impossible to perform the statistical analyses planned in the protocol.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119[2]	119[3]		
Units: Not applicable				
number (confidence interval 95%)	45 (38 to 53)	45 (38 to 53)		

Notes:

[2] - EFS at 3 years on overall population.

[3] - EFS at 3 years on overall population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signature of the consent form until the end of follow-up for the non-serious adverse events and until resolution for the serious adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Arm B - First and second step
Reporting group description: -	
Reporting group title	Arm A

Reporting group description: -

Serious adverse events	Arm B - First and second step	Arm A	
Total subjects affected by serious adverse events			
subjects affected / exposed	149 / 192 (77.60%)	113 / 119 (94.96%)	
number of deaths (all causes)	91	56	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms bening and malignant			
subjects affected / exposed	10 / 192 (5.21%)	9 / 119 (7.56%)	
occurrences causally related to treatment / all	3 / 10	1 / 9	
deaths causally related to treatment / all	2 / 8	1 / 8	
Vascular disorders			
Vascular disorder			
subjects affected / exposed	11 / 192 (5.73%)	11 / 119 (9.24%)	
occurrences causally related to treatment / all	5 / 12	3 / 13	
deaths causally related to treatment / all	1 / 1	0 / 0	
Surgical and medical procedures			
Lung lobectomy			
subjects affected / exposed	1 / 192 (0.52%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

General disorder and administration site conditions			
subjects affected / exposed	24 / 192 (12.50%)	24 / 119 (20.17%)	
occurrences causally related to treatment / all	9 / 35	3 / 29	
deaths causally related to treatment / all	1 / 1	1 / 1	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	10 / 192 (5.21%)	11 / 119 (9.24%)	
occurrences causally related to treatment / all	0 / 13	1 / 14	
deaths causally related to treatment / all	0 / 1	0 / 1	
Reproductive system and breast disorders			
Reproductive system and breast disorder			
subjects affected / exposed	0 / 192 (0.00%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorder			
subjects affected / exposed	26 / 192 (13.54%)	10 / 119 (8.40%)	
occurrences causally related to treatment / all	8 / 33	5 / 12	
deaths causally related to treatment / all	2 / 4	0 / 0	
Psychiatric disorders			
Psychiatric disorder			
subjects affected / exposed	1 / 192 (0.52%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigation			
subjects affected / exposed	5 / 192 (2.60%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Poisoning deliberate			

subjects affected / exposed	1 / 192 (0.52%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	10 / 192 (5.21%)	5 / 119 (4.20%)	
occurrences causally related to treatment / all	2 / 11	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	15 / 192 (7.81%)	13 / 119 (10.92%)	
occurrences causally related to treatment / all	4 / 25	6 / 17	
deaths causally related to treatment / all	1 / 3	1 / 1	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	98 / 192 (51.04%)	86 / 119 (72.27%)	
occurrences causally related to treatment / all	195 / 269	160 / 240	
deaths causally related to treatment / all	0 / 0	1 / 1	
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 192 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	14 / 192 (7.29%)	12 / 119 (10.08%)	
occurrences causally related to treatment / all	3 / 16	3 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorder			
subjects affected / exposed	11 / 192 (5.73%)	22 / 119 (18.49%)	
occurrences causally related to treatment / all	6 / 12	16 / 30	
deaths causally related to treatment / all	1 / 1	3 / 3	
Skin and subcutaneous tissue disorders			
Rash macular			

subjects affected / exposed	1 / 192 (0.52%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorder			
subjects affected / exposed	7 / 192 (3.65%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	1 / 7	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorder			
subjects affected / exposed	3 / 192 (1.56%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	63 / 192 (32.81%)	58 / 119 (48.74%)	
occurrences causally related to treatment / all	33 / 85	39 / 94	
deaths causally related to treatment / all	2 / 6	2 / 5	
Metabolism and nutrition disorders			
Metabolism and nutrition disorder			
subjects affected / exposed	8 / 192 (4.17%)	3 / 119 (2.52%)	
occurrences causally related to treatment / all	2 / 8	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm B - First and second step	Arm A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 192 (0.52%)	0 / 119 (0.00%)	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 192 (0.52%)	0 / 119 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2008	- Modification of typos on protocol and annexes - Updating of listing of investigators
04 March 2009	Updating of listing of investigators : addition of 4 news centers, and 5 news centers realizing graft only
08 November 2010	- Changing the protocol will have more than one treatment arm (arm without Mylotarg®) - Continuation of the ancillary study (resumption of inclusions) - Changing the timing of samples of residual disease (abandonment of post transplant points) and adding a molecular marker.
16 November 2011	- Resumption of inclusions : temporary stop in april 2009, following DMSC opinion who wanted more analysis about safety. Indeed, after the first intermediary analysis (100 patients), one stop criteria seemed to be reached (rate of death in Mylotarg arm), the DMSC requested a new analysis on the 175 patients included at the time, and a stop of inclusion pending result. After this second analysis, none stop criteria was reached. - Precision on treatment diagram : . SCT advisable in case of RCi after first consolidation . SCT regardless of molecular status for blastic patients at J15, and patient with central nervous disorders at diagnose - Modifications in SAE collection for hematological reaction : only unexpected was collected (than 60 days for induction course, and 45 days for consolidations course). - - Updating of listing of investigators.
05 July 2012	- Updating of listing of investigators - Extension of the inclusions period
06 February 2013	Premature stop inclusions
07 February 2014	- Updating of listing of investigators (change of principal investigator in Poitiers) - Modification of term monitoring patients
14 April 2014	- Updating of listing of investigators (change of principal investigator in Colmar) - Modification of expected SAE post graf collection

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 April 2009	Temporary stop in april 2009, following DMSC opinion who wanted more analysis about safety. Indeed, after the first intermediary analysis (100 patients), one stop criteria seemed to be reached (rate of death in Mylotarg arm), the DMSC requested a new analysis on the 175 patients included at the time, and a stop of inclusion pending result. After this second analysis, none stop criteria was reached.	15 December 2009

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25008258

http://www.ncbi.nlm.nih.gov/pubmed/24557850