



Clinical trial results:

Reduced intensity conditioning with high-dose rituximab followed by allogeneic transplantation of hematopoietic cells for the treatment of relapsed/refractory B-cell non Hodgkins lymphomas

Summary

EudraCT number	2007-003657-87
Trial protocol	IT
Global end of trial date	02 February 2017

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	Synopsis 3.0 (Sinossi BCNHL 3.0.pdf)

Trial information

Trial identification

Sponsor protocol code	BCNHL
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fondazione IRCCS Istituto Nazionale Tumori
Sponsor organisation address	Via G. Venezian 1, Milano, Italy, 20133
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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	03 April 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Progression-free survival at one year

Protection of trial subjects:

Not applicable to this patient's population

Background therapy:

High-dose chemoradiotherapy and allogeneic stem cell transplantation (SCT) has been widely used for the treatment of several hematological tumors¹. The procedure was originally proposed as a mean to escalate the doses of chemotherapy and radiation with bone marrow transplantation to restore hematopoiesis. Several lines of evidence indicate that conditioning regimen frequently does not eradicate the malignancy and an immune-mediated graft-versus-tumor effect is important to prevent disease relapse. The most direct demonstration of the graft-versus-leukemia (GVL) effect is the re-induction of complete remission (CR) by the infusion of donor lymphocytes (DLI) in patients who had relapsed after allogeneic stem cell transplantation. This GVL effect takes several weeks to occur

after DLI and presumably requires the persistent engraftment of allogeneic effector cells.

It has been shown that allogeneic SCT is an effective treatment for patients with relapsed/refractory lymphomas. Disease-free survivals (DFS) of 40-50% have been reported in relapsed low-grade lymphomas. A recent report describes the achievement of long-term clinical and molecular remissions after allogeneic SCT in patients with poor prognosis non-Hodgkin's lymphoma. In addition, responses to donor lymphocyte infusions have been documented in patients with chronic lymphocytic leukemia and follicular lymphoma relapsing after allograft. This findings support the notion that allogeneic SCT is an effective salvage treatment and that immune-mediated killing of lymphoma cells is part of therapeutic effect.

Evidence for comparator:

We previously evaluated a population of lymphoma patients transplanted from HLA matched sibling donors with the same conditioning regimen without Rituximab. In that old trial the incidence of acute was GVHD 35%, severe GVHD 14%, and of chronic was GVHD 49% (extensive GVHD 25%).

Actual start date of recruitment	31 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	Italy: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	121
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From Oct 2007 to Oct 2015, 121 patients were enrolled. The median age was 52 yrs. Diagnoses were de novo or transformed DLCL, and indolent lymphomas. 67 out of 121 underwent tx from a related sibling and 54 received a graft from an unrelated donor. 12 patients had mismatches in class I and the rest in class II. Only 3/20 pts had mism. in locus C

Pre-assignment

Screening details:

we excluded patients with diagnosis not included in the inclusion criteria

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm
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Arm description:

This is a single arm, prospective, phase II study investigating the effect of a single dose of rituximab in combination with a RIC regimen on PFS in refractory/relapsed B cell lymphomas. In addition, overall survival, incidence of acute and chronic GVHD, and GVHD-free relapse survival were evaluated.

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

Dosage and administration details:

Enrolled patients were treated with salvage rituximab chemotherapy at time of relapse. The choice of the salvage regimen was left to center preference. Then the patients received the following drug as conditioning regimen: rituximab (500 mg/m², day -6), thiothepa (6 mg/kg every 12 hrs for 2 doses, day -5), cyclophosphamide (30mg/kg, days -4 and -3), and fludarabine (30 mg/m², days -4 and -3, administered 4 hrs after cyclophosphamide). The choice to administer one single dose of rituximab relies on the assumption that circulating CD20+ B cells of the recipient had already been depleted by rituximab-supplemented salvage chemo-immunotherapy, whereas pretransplantation rituximab will probably work largely by depleting the donor's alloreactive B cells.

Number of subjects in period 1	Single arm
Started	121
Completed	121

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	121	121	
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)	121	121	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
All subjects were 23 to 65 years			
Units: years			
median	52		
full range (min-max)	23 to 65	-	
Gender categorical			
Units: Subjects			
Female	41	41	
Male	80	80	

Subject analysis sets

Subject analysis set title	All patients
Subject analysis set type	Full analysis

Subject analysis set description:

One hundred twenty-one patients with relapsed/refractory lymphoma were enrolled in this multicenter, prospective, phase II trial (refer to Table 1 for baseline characteristics of patients). The median age was 52 years (range, 24 to 65 years). Diagnoses were de novo or transformed DLBCL (n = 35, of which 2 transformed and 33 de novo), MCL (n = 22), and indolent lymphomas (FL, n = 35; CLL/SLL, n = 29). Sixty-seven out of 121 (55%) underwent transplantation from a related sibling (1 mismatched siblings in only 2 cases) and 54 (45%) received a graft from an unrelated donor (34 matched, 20 mismatched). Twelve patients had mismatches in class I and the rest had mismatches in class II. Interestingly, only 3 patients out of 20 (15%) had antigenic mismatches at locus C. It is important to note that most of the patients had a chemosensitive disease (complete remission [CR], n = 48 [39%]; partial remission, n = 61 [51%]) at transplantation.

Reporting group values	All patients		
Number of subjects	121		
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)	121		
From 65-84 years	0		
85 years and over	0		
Age continuous			
All subjects were 23 to 65 years			
Units: years			
median	52		
full range (min-max)	23 to 65		
Gender categorical			
Units: Subjects			
Female	41		
Male	80		

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description: This is a single arm, prospective, phase II study investigating the effect of a single dose of rituximab in combination with a RIC regimen on PFS in refractory/relapsed B cell lymphomas. In addition, overall survival, incidence of acute and chronic GVHD, and GVHD-free relapse survival were evaluated.	
Subject analysis set title	All patients
Subject analysis set type	Full analysis
Subject analysis set description: One hundred twenty-one patients with relapsed/refractory lymphoma were enrolled in this multicenter, prospective, phase II trial (refer to Table 1 for baseline characteristics of patients). The median age was 52 years (range, 24 to 65 years). Diagnoses were de novo or transformed DLBCL (n = 35, of which 2 transformed and 33 de novo), MCL (n = 22), and indolent lymphomas (FL, n = 35; CLL/SLL, n = 29). Sixty-seven out of 121 (55%) underwent transplantation from a related sibling (1 mismatched siblings in only 2 cases) and 54 (45%) received a graft from an unrelated donor (34 matched, 20 mismatched). Twelve patients had mismatches in class I and the rest had mismatches in class II. Interestingly, only 3 patients out of 20 (15%) had antigenic mismatches at locus C. It is important to note that most of the patients had a chemosensitive disease (complete remission [CR], n = 48 [39%]; partial remission, n = 61 [51%]) at transplantation.	

Primary: PFS

End point title	PFS
End point description: Endpoint was 1 year progression free survival. We expected an improvement of 1 year PFS from 70% to 77%. To obtain this result, a total sample of 190 patients was required.	
End point type	Primary
End point timeframe: at 3 years post transplant	

End point values	Single arm	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	121	121		
Units: 145	121	121		

Statistical analyses

Statistical analysis title	Statistical analysis plan
Statistical analysis description: The incidence of NRM, relapse, and acute and chronic GVHD were estimated in a competing risks setting using cumulative incidence estimates and the curves were compared by means of the Gray test. In the estimation of GVHD, death without GVHD was evaluated as a competing event. NRM and relapse were competing events for each other [Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16:1141-1154]	

We also tested the composite endpoint GRFS [

Comparison groups	Single arm v All patients
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	> 0.05 ^[2]
Method	t-test, 1-sided
Parameter estimate	difference in PFS
Point estimate	190
Confidence interval	
level	Other: 80 %
sides	1-sided
lower limit	70
Variability estimate	Standard error of the mean

Notes:

[1] - no treatment effect on NRM and a 35% relative improvement of relapse rate (from 20% to 13%), at a significance level of 10% (1-sided test) a sample size of 190 assessable patients ensured a 80% probability of detecting a 70% to 77% increase in 1-year PFS. However, because of the expansion of trials incorporating novel agents and an increase of haploidentical donor use, the accrual rate decreased in the last 2 years and the data safety and monitoring committee suggested to stop

[2] - no treatment effect on NRM and a 35% relative improvement of relapse rate (from 20% to 13%), at a significance level of 10% (1-sided test) a sample size of 190 assessable patients ensured a 80% probability of detecting a 70% to 77% increase in 1-y

Secondary: Incidence of acute graft-versus-host disease (aGVHD) within 100 days

End point title	Incidence of acute graft-versus-host disease (aGVHD) within 100 days
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End point description:

Acute GVHD were estimated in a competing risks setting using cumulative incidence estimates and the curves were compared by means of the Gray test

End point type	Secondary
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End point timeframe:

100 days

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	121			
Units: Cumulative incidence	121			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of chronic graft-versus-host disease (cGVHD) within 100 days

End point title	Incidence of chronic graft-versus-host disease (cGVHD) within 100 days
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End point description:

Chronic GVHD were estimated in a competing risks setting using cumulative incidence estimates and the curves were compared by means of the Gray test

End point type	Secondary
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End point timeframe:

Between 101 days and 3 years from allogeneic transplantation

End point values	Single arm	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	121			
Units: Cumulative incidence	121	94		

Statistical analyses

No statistical analyses for this end point

Secondary: Nonrelapse mortality at one year

End point title	Nonrelapse mortality at one year
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End point description:

The incidence of NRM was estimated in a competing risks setting using cumulative incidence estimates and the curves were compared by means of the Gray test. Relapse was competing event for NRM.

End point type	Secondary
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End point timeframe:

One year from allogeneic transplantation

End point values	Single arm	All patients		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	121	121		
Units: Cumulative incidence	121	121		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Post transplantation toxicities were reported as infections or complications after engraftment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	3.0
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Reporting groups

Reporting group title	all patients
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Reporting group description: -

Serious adverse events	all patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 121 (32.23%)		
number of deaths (all causes)	42		
number of deaths resulting from adverse events	24		
Investigations			
CMV reactivation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
ictus			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombotic microangiopathy			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			

Encephalitis alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: fever in encephalitis of not determined etiology		
	1 / 121 (0.83%)		
	1 / 1		
	1 / 1		
neurological impairment alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all			
	1 / 121 (0.83%)		
	1 / 1		
	0 / 0		
Blood and lymphatic system disorders Disease progression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all			
	9 / 121 (7.44%)		
	0 / 8		
	0 / 9		
General disorders and administration site conditions fever of unknown origin alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: FUO in non neutropenic patient		
	1 / 121 (0.83%)		
	1 / 1		
	0 / 0		
Septic shock alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: 1 septic shock occurred during Zevalin treatment for disease progression		
	3 / 121 (2.48%)		
	1 / 3		
	1 / 2		
transplant related mortality alternative assessment type: Systematic subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all			
	1 / 121 (0.83%)		
	1 / 1		
	1 / 1		
relapse of original disease alternative assessment type: Systematic			

subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
renal and respiratory impairment	Additional description: and cerebral haemorrhage		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
aGVHD	Additional description: steroid dependent aGVHD /encephalitis		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Headache	Additional description: headache with fever and cytopenia		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Acute respiratory failure	Additional description: due to pulmonary GVHD		
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonia	Additional description: 1 Pneumonia in refractory CLL. 6 Pneumonia		
alternative assessment type: Systematic			

subjects affected / exposed	7 / 121 (5.79%)		
occurrences causally related to treatment / all	6 / 7		
deaths causally related to treatment / all	4 / 5		
GVHD	Additional description: 2 pulmonary GVHD, 1 corticosteroid refractory aGVHD		
alternative assessment type: Systematic			
subjects affected / exposed	4 / 121 (3.31%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	1 / 4		
Hepatobiliary disorders			
hepatic toxicity			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
AST and ALT increase			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
VOD	Additional description: veno-occlusive disorder		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Cystitis haemorrhagic			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 121 (2.48%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
tubular	Additional description: tubular necrosis		
alternative assessment type: Systematic			

subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
vertebral fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
CVC infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
cerebral cryptococcosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
sepsis	Additional description: form E. Coli		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
pulmonary infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	all patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 121 (16.53%)		
Infections and infestations			
infections	Additional description: a detailed description of non serious adverse event was not available		
alternative assessment type: Systematic			
subjects affected / exposed	20 / 121 (16.53%)		
occurrences (all)	20		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2009	Text changes (New text in bold; deleted text in italics) Synopsis " IC":pag.6 for identical sibling and age $\geq 18 \leq 60$ years in case of matched unrelated donor; Synopsis" IC" pag.6 Unrelated donor fully HLA matched at locus HLA-A, HLA-B, HLAC, HLA-DRB1, HLA-DQB1 as evaluated by high resolution typing Synopsis "TP" pag.7 Conditioning regimen for identical sibling or unrelated donor Synopsis "TP"pag.7 Patients with related sibling with a class I antigen mismatch or with unrelated donor will receive rabbit anti-thymocyte globulin.(Thymoglobuline 3.5 mg/kg daily on days - 4 and - 3) "Rationale " pag.9 Treatment-related mortality and survival, for recipients of unrelated grafts, has declined significantly over the years. Improvements in HLA matching, better supportive care particularly in infection management, and better GVHD prophylaxis and treatment, and the recent introduction of RIC have probably played roles in the reduction of NRM. In fact, for patients who received myeloablative unrelated donor transplants as a first transplant, there was a significant improvement in NRM from earlier period (1990-2002) to recent period (2003-2006) [1-year NRM 48% versus 32% versus 20% for patients receiving myeloablative conditioning in earlier period versus recent period versus RIC in recent period, respectively]. For this reason, we have decided to include also patients having a matched unrelated donor (in absence of HLA identical sibling) Inclusion criteria 1) Age $\geq 18 \leq 65$ years in case of identical sibling donor 2) Age $\geq 18 \leq 60$ years in case of matched unrelated donor 6)Unrelated donor fully HLA matched at locus HLA-A, HLAB, HLA-C, HLA-DRB1, HLA- DQB1 as evaluated by high resolution typing (it is acceptable one allelic mismatched at class I) "TP" pag 11. Conditionin

18 July 2012	This amendment involved the following sections: 1) Extension of enrollment period: given the enrollment rate below planned numbers, it was decided to enroll 40 more patient in the following 2 years. After the next IMDC it will be decided to prolong enrollment period. protocol page 4, synopsis page 1 and IC were modified. 2) insurance coverage extension: since at first protocol approval insurance was not required, principal investigator decided to implement insurance coverage as for Ministerial decree 14.07.2009. 3) Informed consent for personal data protection: it was included a specific section for personal data protection as per decree dated 24/07/2008. Informed consent was modified. 4) Inclusion of patients with indolent lymphoma (lymphocytic lymphoma/CLL, FL, Marginal Nodal Lymphoma) having PD at allo-TX: latest available data proved benefits from allo-Tx in patients with indolent lymphoma. The following IC were edited as indicated: 2c) FCL and MZL lymphoma relapsing after 2 lines or relapsing after auto-SCT; 2d) Primary refractory MCL e MZL; 2g) CLL, FCL, MCL, MZL and DLBCL considered eligible for high-dose chemotherapy, with a positive bone marrow biopsy or collecting PCR positive harvests before the autografting phase. 5) Minimum criteria for unrelated mismatched donors. Protocol was amended to include patients with HLA as per IBMDR. 6) Inclusion of patients with age up to 65yrs with HLA matched unrelated donor. 7) ATG administration: considering better tolerability of ATG in terms of reduction of IRR, administration was started since day 4. Dosage: 0.5mg/kg day -4, 3 mg/kg day -3 and 3.5mg/kg day -2. Total dosage remains unchanged. 8) Modification of participant centers. 9) Integration in the ICF of informations contained in the paragraph "Cautions required by being a trial participant" 10) It is specified that administrative management and monitoring of the study is done by Clinical Trial Center and "Fondazione IRCCS Istituto Nazionale dei Tumori"
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28390983>