PHASE II STUDY OF YTTRIUM-90-IBRITUMOMAB TIUXETAN IN REDUCED INTENSITY CONDITIONING (RIC) ALLOGENEIC TRANSPLANT IN RELAPSED OR REFRACTORY AGGRESSIVE B-CELL LYMPHOMA: A GEL/TAMO PHASE II CLINICAL TRIAL

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BACKGROUND AND OBJECTIVES: Radiolabelled immunotherapy is a promising treatment in malignant lymphomas, also as a part of conditioning regimen for allogeneic stem cell transplant (AlloSCT). We designed a Phase II clinical Trial with Yttrium-90 (Y-90)-ibritumomab tiuxetan as a part of a RIC regimen associated with Melphalan and Fludarabine (Clinical Trials Identifier: NCT00644371). The ~~main objective~~primary end-point was ~~to evaluate one~~1-year p~~P~~rogression free s~~S~~urvival (PFS), and secondary ~~objectives~~end-points were: toxicity, engraftment, acute and chronic GVHD and ~~one~~ 1-year non relapse mortality (NRM) and overall survival (OS).

PATIENTS AND METHODS: 20 patients from 10 Spanish centers with aggressive non-Hodgkin's lymphoma (NHL), including diffuse large B-cell, follicular grade 3, Burkitt's and mantle-cell lymphomas, were eligible for the trial. Inclusion criteria were: to reach less than a partial response (PR) after two lines of chemotherapy, relapse after an autologous SCT (ASCT), positive PET scan ~~before or~~ after ASCT, or PBSC mobilization failure~~ in mobilization of stem cells for ASCT~~. Conditioning regimen consisted of rituximab 250 mg (day -21 and -14), Y-90 ibritumomab IV (0.4mCi/Kg, day -14) plus f~~F~~ludarabine 30 mg/m^2 IV (days -3,-2) plus m~~M~~elphalan 70mg/m^2 IV (days-3,-2) or only -2 plus thiotepa 10 mg/kg (day -8) in case or relapse after autologous stem cell transplant in the last 6 months before AlloSCT. All donors were family matched.

RESULTS: Median age was 50 years (range 32-63). At ~~the moment of~~ transplantation, 7 patients (39%) were in complete remission (CR), 7 (33%) in PR and 4 (28%) were chemo-refractory to last line of therapy. Ten patients (56%) had a prior ~~ASTC~~ASCT. Y-90 ibritumomab infusions were well

tolerated, without immediate reported adverse reactions. All patients engrafted, and median of days to reach more than 500x10^9 granulocytes and more than 20x10^9 platelets were 15 (12-24) and 12 (2-19) respectively. Cumulative incidence of grade 2-4 acute GVHD was 50%. With a median follow-up of 46 months (39-55), 8 patients (44.4%) are alive, all of them disease-free. Four years estimated OS and PFS by Kaplan-Meier were both 44.4%; disease status at transplant and achieving CR at day +100 had both significant impact on survival. Day +100 and 1 year NRM were 16% and 28% respectively.

CONCLUSIONS: Our results show that yttrium-90-ibritumomab tiuxetan as a component of reduced intensity conditioning for allogeneic transplantation is feasible and safe in patients with high-risk relapsed or refractory aggressive B-cell lymphoma, and results in an ~~non-despicable~~appreciable survival rate for these poor prognosis patients. Development of further phase III clinical trials should clarify the exact contribution of RIT to conventional RIC AlloSCT.

INTRODUCTION

Allogeneic stem cell transplant (AlloSCT) is a potential curative option for patients with non-Hodgkin lymphomas (NHL), based on the addition of an immune-mediated graft-versus-lymphoma effect (GVLE) to the traditional cytotoxic treatments, that allows us to achieve long-term remissions (1-3), even in patients in whom salvage chemotherapy or autologous stem cell transplant have failed. However, post-transplant relapse ~~keeps~~ continues to be ~~as~~ a major cause of failure of this procedure (4) and it is even higher if we focus on chemo-~~r~~refractory diseases or higher risk patients (5). Conditioning regimen may play an important role on early disease control until an effective GVLE appears, but usually candidates to AlloSCT are heavily pre-treated patients, have a previous autologous stem cell transplant or are too old, so they cannot receive a conventional myeloablative conditioning regimen. In these situations, non-myeloablative AlloSCT is an alternative, but relapse rate are higher with this reduced intensity conditioning (6), so new drugs should be introduced on it to improve the results.

Radioimmunotherapy (RIT) with Ytrium-90 ibritumomab tiuxetan (Y-90-IB) has been one of the last promising approaches in the treatment of CD20 positive malignancies, based on the bind of the radioisotope Ytrium 90 (Y-90) to a murine antibody that targets CD20 (ibritumomab). This drug has been used in the treatment of relapse/refractory NHL, achieving an 80% of overall response rate (ORR) and 20% of complete remission (CR) rate in the first phase III clinical trial (7), and has been included as well on autologous stem cell transplant conditioning regimen (8, 9). However, none of these approaches are curative treatments for indolent lymphomas, and continue to be insufficient for some aggressive lymphoma. In order to manage relapse after conventional chemotherapy or autologous stem cell transplant, radio-immunotherapy has been proposed as a part of reduced intensity conditioning AlloSCT. Our hypothesis is that this strategy can enhance initial cytotoxic effect of conditioning regimen so GVLE can later control the disease in those higher relapse risk patients. To explore this effect of the addition of Y-90-IB to a non-myeloablative conditioning regimen with

fFludarabine and mMelphalan in AlloSCT, both in terms of survival and toxicity, GELTAMO group designed a phase II multicentre clinical trial. Hereby we report the long-term follow up results of the cohort with a median follow up of 4 years after AlloSCT.

PATIENTS AND METHODS

Study Design and Aims

This study is a phase II multicenter clinical trial designed to analyse efficacy and toxicity of Y-90-IB in the context of AlloSCT in CD20 positive NHL patients. The study was registered at www.clinicaltrials.gov as NCT 00644371. The clinical trial was conducted under the Ethical Principles for Medical Research Involving Human Subjects included in the World Medical Association Declaration of Helsinki and it was approved by every local ethics committee. Written informed consent was obtained from all patients for the study following ~~the~~ Good Clinical Practice rules.

Primary endpoint was ~~to evaluate~~ progression free survival (PFS), and secondary endpoints were ~~analyse~~ toxicity, overall survival rate (OS), relapse rate (RR) and incidence of acute and chronic GVHD.

Adverse events were notified by the official form of “serious and unexpected adverse reaction occurred in Spain” (RD 223/204), as well as recorded in the protocol case record form (CRF).

Patient selection

Patients with diagnosis of CD20 positive NHL, including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Burkitt’s lymphoma (BL) or grade 3b or transformed follicular lymphoma (FL) were considered for the study. Inclusion criteria were: achieving less than a partial response (PR) after 2 lines of treatment, relapse after autologous stem cell transplantation, positive PET after autologous stem cell transplantation or stem cell mobilization failure. Patients were eligible if they were between 18 and 65 years old, ECOG performance status was ≤2 and no major organ dysfunction was present (serum bilirubin < 2 mg/dL with AST, ALT, GGT and AP < 2

times ULN, left ventricular ejection fraction > 40% and serum creatinine < 2 mg/dL). Exclusion criteria included prior RIT, HIV associated lymphoma, pregnancy or breast feeding, severe comorbidities or known allergy to murine antibodies or Y-90.

Treatment protocol

Patients received rituximab at 250 mg/m^2 on days -21 and -14, and 0.4 mCi/kg of Y-90-IB was administered after rituximab dose. Conditioning regimen consisted of fludarabine 30 mg/m^2 on days -7 to -3, and melphalan 70 mg/m^2 on days -3 and -2. In case of patients relapsing after an autologous stem cell transplant including melphalan within the last 6 months, thiotepa 5 mg/kg was added on day -8 –(**Figure 1**).

Comentado [IJ1]: Maximum dose?

Graft versus host disease (GVHD) prophylaxis consisted of cyclosporine A (CSPA) and methotrexate (MTX). Intravenous CSPA was given at dose of 0.25 mg/Kg from day -7 to -2, 1.5 mg/Kg from day -1 to +1 and adjusted to blood levels afterwards. CSPA levels were determined on peripheral blood twice a week. After discharge, patients received CSPA p.o. twice a day and it was tapered down on day +56 in absence of GVHD. Methotrexate followed by folic acid was administered intravenously on day +1 (15 mg/m^2), +3, +6 and +11 (10 mg/m^2).

Antimicrobial prophylaxis and supportive treatment were administered according to the standard of care of each center.

Patients were evaluated for clinical response at day +100, +180 and +1 year after AlloSCT and every 6 months up to 2 years. Responses were scored using standard criteria (10).

Statistical Analysis

Data analyses were performed using SAS software (SAS Institute, v9.1.3, Cary, NC) and SPSS v.20 (IBM, Endicott, NY). PFS was defined as time from AlloSCT to progression or death from any cause.

OS was defined as time from the moment of AlloSCT to death from any cause. Estimated PFS and OS curves were calculated by non-parametric Kaplan-Meier method, and the log-rank test was used to test statistical significance of every variable on survival data. Patients were censored at day +100 for acute GVHD and when considering chronic GVHD for any survival analysis, we conducted a landmark analysis at day +100. A multivariate analysis was not developed because of the limited number of patients. Cumulative incidence was calculated for relapse rate and GVHD considering death from any other cause as a competitive risk (11). Differences were considered statistically significant with a ~~p~~ *P* value ~~of~~ ≤0.05.

RESULTS

Twenty patients were enrolled in the clinical trial in 10 referral centers for AlloSCT in Spain between June 2008 and April 2010; There were 2 non-evaluable patients, one of them due to disease progression before AlloSCT (the patient received the same conditioning regimen with (Y-90)-ibritumomab tiuxetan off protocol) and another one due to renal failure (he did not received the drug), so eighteen patients were ~~finally~~ eventually considered evaluable; Median age was 50 (range 32-63) and 44% of patients were older than 55. Diagnosis were diffuse large B cell lymphoma (n=6), mantle cell lymphoma (n=5), follicular lymphoma grade 3b (n=4), transformed follicular lymphoma (n=2) and Burkitt's lymphoma (n=1). Main patient~~'s~~ characteristics are listed on **Table1**.

Patients had received a median of 3 previous lines of chemotherapy (range 2-5), and 45% of them received 4 or more previous treatments. Ten patients (60%) had ~~undergone~~ a previous ~~autologous stem cell transplant~~ASCT. Eleven patients (61%) had active disease before performing the AlloSCT: partial response in 6 (33%) and stable disease in 5 (28%). The remaining 7 (39%) were in complete remission (CR) at the moment of the AlloSCT, 1 in first CR and 6 in second or subsequent CR.

Engraftment and immune reconstitution: The median of days to reach more than $500x10^9$ granulocytes and more than $20x10^9$ platelets were ~~+~~15 (range 12~~—~~24) and ~~+~~12 (range 2-19) respectively. All patients engrafted and no cases of graft failure were documented. At last follow up, 100% of alive patients had achieved a CD4 count higher than 400/uL.

Donor and stem cells source: Donor was HLA-matched sibling in 100% of patients, and G-CSF mobilized-peripheral blood (n=17) or bone marrow (n=1) unmanipulated hematopoietic stem cells ~~without any manipulation~~ were infused on day 0.

Graft Versus Host Disease (GVHD): Thirteen patients (72.3%) developed acute GVHD (aGVHD), with a median onset of 34 days (12-82). Incidence of grade 2-4 aGVHD was 50% and grade 3-4 aGVHD affected 4 patients (22%).

Chronic GVHD (cGVHD) was present in 7 of 12 evaluable patients (59%) and median day of cGVHD appearance was 343 (122-626); ~~three~~ 3 ~~patients~~ (25%) developed limited cGVHD, and 4 (33%) extensive cGVHD. In 2 patients, cGVHD appeared after withdrawal of immunosuppression or DLI because of disease relapse or progression.

At last follow up, 6 out of 8 (75%) alive patients had discontinued immunosuppressionе~~d treatment~~ and did not present signs of active cGVHD.

Response: At day +100, we observed disease response in 10 out of 14 evaluable patients (71.5%), with 9 CR and 1 PR. Among the 11 patients with active disease (PR or SD) before AlloSCT, overall response rate was 36% (27% of CR) at day +100. Regarding to different diagnosis, CR rate was 75% for FL, 60% for MCL and 50% for DLBCL. In the group of BL and transformed FL patients, any CR was documented. **Table 2** shows evolution on response during the follow up.

In 4 patients, revaluation at day +100 showed progression disease. And in another 4 cases, relapse or progression were documented during the follow up, resulting in an estimated cumulative incidence of relapse or progression of 26% at 4 years (**Figure 2c**); all of them relapsed or progressed early post-transplant, with a median of 3 months (1-3) after AlloSCT. Among these relapsing-progressing patients, disease status at the moment of the AlloSCT was CR in 1, PR in 1 and SD in 2.

Four patients were not evaluated because of early deaths before day +100 (2 cases of invasive fungal ~~infectious~~ disease, 1 septic shock and 1 acute GVHD), all of them had refractory disease before AlloSCT.

Progression free and Overall Survival: With a median follow up of 46 months (39-55), 8 patients (44.4%) are alive, all of them disease-free.

Four-~~-~~year~~s~~ estimated OS and PFS by Kaplan-Meier were both 44.4% (**Figure 2a and 2b**). On the univariate Kaplan-Meier / log rank test analysis, CR status at ~~the moment of~~ transplant showed to have significant influence on 4-~~-~~year~~s~~ estimated PFS (71% vs 27%; ~~*p*~~*P*=0.04~~6~~) and OS (71% vs 27%; ~~*p*~~*P*=0.04~~7~~). Development of acute GVHD is associated also with poorer OS (67% vs 22% for less than grade 2 aGVHD or 2-4 aGVHD), although differences ~~is~~ were not statistically significant (~~*p*~~*P*=0.07~~7~~). (**Figure 3**)

Comentado [IJ2]: Redondear decimales

Early post AlloSCT response also showed to be an important variable with impact on both OS and PFS in a landmark analysis at day +100. Those patients who did not achieve CR at day +100 had a poor prognosis both for OS (89% vs 20%; ~~*p*~~*P*<~~=~~0.001~~0~~) and PFS (89% vs 0%; ~~*p*~~*P*<~~=~~0.001~~0~~).

Overall and Non Relapse Mortality: Overall mortality was 55.6% (n=10). Five patients died due to infectious ~~disease~~complications; in 3 of them, infection occurred in the early post-AlloSCT period, with 2 invasive aspergillosis (one of them in a patient with active aGVHD) and a septic shock. The two remaining cases of fatal infection ~~disease~~ were 1 case of pneumonia in a patient with active disease at day +100 and a viral meningitis ~~1~~one ~~-~~year post-AlloSCT. One patient died due to acute GVHD. Progression or relapse was the cause of death in the remaining 4 patients (22%). Mortality rate was higher among those patients with poorer prognosis according to disease status (29% for CR patients vs 80% for patients with PR/SD at the moment of AlloSCT; ~~*p*~~*P*=0.06~~7~~).

Estimated NRM at day +100 and 1-year post-AlloSCT was 16% and 28% respectively, with an overall NRM of 33% (n=6) after 4 years follow up (**Figure 2d**). Age over 55 was the main prognostic factor for NRM; patients older than 55 had higher NRM (37.5% vs 10% at day +100; *p*=0.039). Presence of grade II-IV aGVHD (44% vs 11% at day +100; ~~*p*~~*P*=0.07~~4~~) and CR at the moment of the AlloSCT (0% vs 37% at day + 100; *p*=0.136) were also associated with a trend ~~of~~ for higher NRM.

Conditioning Toxicity:

The 100% of patients received the scheduled doses of treatment included in the conditioning regimen, with no dose reductions either in Y-90-IB or in the conventional drugs. Y-90-IB infusions were well tolerated, without immediate ~~reported~~ adverse reactions. Regarding to adverse events, 11 cases with grade III-IV (according to Common Toxicity Criteria) were notified; Grade III toxicities ~~comprised~~ included diarrhea, CMV enteritis, chronic renal failure exacerbation, congestive heart failure (2 cases), pleural effusion and gland infection. Grade IV adverse events were 2 cases of pneumonia and 2 cases of septic shock. None of these adverse events were clearly related with drug administration, but common adverse events in the ~~context~~ setting of AlloSCT.

DISCUSSION

Hereby we present a multicentre phase II clinical trial in which Y-90-IB was included as a part of a non-myeloablative conditioning regimen with m~~M~~elphalan and f~~F~~ludarabine for higher risk NHL, in order to increase antitumor effect and control disease early post-AlloSCT without adding significant toxicity. The results of this study support the feasibility and safety of Y-90-IB, achieving an acceptable PFS and OS rate considering the high risk ~~patients characteristics~~features, and with an excellent toxicity profile of the drug in terms of adverse events.

Patients included in this phase II study had a very poor prognosis: diagnosis were grade 3 FL, MCL, DLBCL or Burkitt lymphoma; 61% of them has active disease before AlloSCT, including about 30% of patients who did not achieve even a partial response with the last chemotherapy course before undergoing AlloSCT, and 56% of them had relapsed after a previous autologous stem cell transplant. After a median follow up of 46 months, 44.4% of patients are alive and disease free. At day +100, 71.4% of the patients were in CR, which could be related with the increment of antitumor effect due to the combination of Y-90-IB with a conventional RIC regimen. Among those patients who underwent AlloSCT with persistent disease (PR or less than PR), overall response rate was 36%, with a 27% of CR. According to our results, not only disease status at AlloSCT has an impact on PFS/OS, but also this early disease control after the AlloSCT is essential, since any patient among those who achieved CR at day +100, had further relapsed of their primary disease. It is accepted that

chemosensitive patients have better outcome after AlloSCT, especially for those histologies that are less sensitive to graft versus lymphoma effect (3, 5, 12). In addition, the impact of day +100 response in our series, that is consistent with the report by Gopal et al (13), would support the role of RIT for achieving an early disease control that could be later completed by a long-term immune-mediated disease control.

Complementary to the early disease control provided by the conditioning regimen, graft versus lymphoma effect (GVLE) was also supported by our results given that our long-term follow up (median of 46 months) is the longest one reported in a clinical trial of Y-90-IB containing RIC regimen for aggressive B-NHL by the moment. Although numbers are small, these data allows us to consider late relapses in this group of patients. At the time of the last analysis, any late relapse was documented, which support the role of GVLE in patients who had already failed after some high dose chemotherapy regimen or autologous stem cell transplant.

In our series we observed an estimated NRM of 28% at 1 year after AlloSCT. This data is probably related with the percentage of higher risk patients included in the study, since NRM for young and good-prognosis patients, is significantly lower (0% for patients who underwent AlloSCT in CR). Regarding to GVHD, we report a cumulative incidence of 50% for grade II-IV acute GVHD, and 59% for chronic GVHD. Although fatal GVHD rate is low (6%), this group of patients trends to have a higher NRM, probably related to GVHD associated comorbidity. Regarding to cGVHD, at last follow up, 75% of patients had discontinued immunosuppressive therapy and they are free of cGVHD signs or symptoms. It is difficult to compare these NRM and GVHD data with other series due to the heterogeneity of patients included, with different diagnosis, pre-AlloSCT status and GVHD prophylaxis regimens. Considering those that included aggressive lymphomas, and or chemorefractory patients, in whom graft versus lymphoma effect should be forced with an early immunosuppression therapy withdrawal, results are similar to our series in Shimani et al or Bethge et al (14-16). On the other hand, the inclusion of indolent lymphomas or the addition of ATG in the GVHD prophylaxis together with the lower risk patients included can contribute to decrease both aGVHD and NRM in some other series (17-19). It seems therefore quite clear now that the addition of Y-90-IB by itself is

not associated with a higher GVHD. In the most recent report from Khouri et al (18), which differs from ours in the inclusion criteria (it included 26 FL), and from Bouabdallah et al. (19), which did not include refractory patients, grade II-IV aGVHD cumulative incidence was 23% and 27%. Nonetheless, the first clinical trial published by Shimoni et al (15), where all the patients had persistent disease at the moment of AlloSCT, showed up to 62% of aGVHD cumulative incidence. (Table 3)

Y-90-IB has also been employed after ASCT and our prior report of the efficacy of Z-BEAM in refractory patients after ASCT (8) tell us about the efficacy of RIT with 70% of CR at day +100 and an estimated OS and PFS of 63% and 61% respectively in the relapse/refractory aggressive lymphoma setting. The election of ASCT or AlloSCT with Y-90-IB in these poor prognosis patients is an unanswered question and perhaps a trial with a randomization based on the existence or not of a suitable donor should be considered.

In conclusion, ~~upon our results, we can say that~~ the incorporation of Y-90-IB to the RIC regimen is safe and results in appreciable PFS in patients diagnosed with poor prognosis aggressive B-NHL. Status of the disease at transplant is an important issue and new agents should be incorporated in the pretransplant period in order to improve efficacy after allogeneic transplant. Based on these data future research with Y-90-IB in the transplant setting is wgu~~u~~arranted.

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Table 1. Patient~~'s~~ characteristics

CHARACTERISTIC	N = 20
Median age (range)	50 (32-63)
Sex	
Female	3 (17%)
Male	15 (83%)
Diagnosis; n (%)	
Follicular lymphoma (FL)	4 (22%)
Transformed FL	2 (11%)
Diffuse Large B cell lymphoma (DLBCL)	6 (33%)
Mantle cell lymphoma (MCL)	5 (28%)
Burkitt lymphoma (BL)	1 (6%)
Previous lines of therapy	
Two	3 (17%)
Three	7 (39%)
Four	5 (28%)
Five	3 (17%)
Previous Autologous Stem Cell Transplant	10 (56%)
Related Donor	18 (100%)
Disease status at ~~Allogeneic Stem Cell t~~Transplant	
Complete remission (CR)	7 (39%)
Partial Response (PR)	6 (33%)
Stable Disease (SD)	5 (28%)

Comentado [IJ3]: Por orden de frecuencia

Comentado [IJ4]: Por orden de frecuencia

Comentado [IJ5]: Podría suprimirse

Table 2. Disease response

Status at AlloSCT	Response at day +100	Status at last follow up	Cause of death
CR 7	CR 6	Alive in CR 5	
		Death while in CR 1	Viral encephalitis
	Relapse 1	Death	Relapse ~~of the primary disease~~
PR 6	CR 2	Alive in CR 2	
	PR 1	Death while in PR	Pneumonia (*Pseudomonas*)
	Progression 1	Death	Disease p~~P~~rogression ~~of the primary disease~~
	Non evaluable 2	Death before +100	Invasive a~~A~~spergillosis
SD 5	CR 1	Alive in RC	
	Progression 2	Death	Disease p~~P~~rogression ~~of the primary disease~~
	Non evaluable 2	Death before +100	Septic shock
			Acute GVHD

Con formato: Fuente: Cursiva

Table 3.

Comentado [IJ6]: Falta tí

	N	~~Comments~~Patient characteristics	Response to transplant	Median FU	OS/PFS	aGVHD	cGVHD	NRM
Shimoni et al. (Bone Marrow Transpl. 2008)	12	All of them active disease before AlloSCT	CR+PR 83%	21 months	2 years: 33%/33%	Gr. II-IV: 67% Gr. III-IV: 50%	57%	42%
Bethge et al. (Blood 2010)	40	DLBCL or transformed lymphoma not included	CR 62% PR 32%	672 days	2 years: 51%/43%	Gr. II-IV: 43%	53%	45%
Abou Nassar et al. (Bone Marrow Transpl. 2010)	12	10 FL and 2 transformed FL	CR 67%	31 months	2 years: 83%/74%	25%	63%	18%
Gopal et al. (Blood 2011)	40	Includes 14 DLBCL	CR 35% PR 25%	1.7 years	30 months: 54%/31%	Gr. I-III: 78% Gr. III: 10% No grade IV	20%	16%
Bethge et al. (BMT 2012)	20	All of them aggressive lymphomas	CR 45% PR 5%	1115 days	3 years: 20%/20%	Gr. II-IV: 45%	70%	30%
Khouri et al. (Blood 2012)	26	All of them FL, 60% in CR/PR	CR 96%	33 months	3 years: 88%/85%	Gr. II-IV: 23%	39%	8%
Bouabdallah et al. (Ann. Onc. 2015)	31	Includes 14 DLBCL and 5 transformed FL. All in CR/PR	----	32 months	2 years: 80%/80%	Gr. II-IV: 27%		13%
GELTAMO series (present)	18	Includes high grade NHL	ORR 71.5% CR 64%	46 months	4 years: 44.5%	Gr. II-IV: 50% Gr. III-IV: 22%	59%	28%

N = number of patients included; FU: follow up; aGVHD: acute graft versus host disease; cGVHD: chronic graft versus host disease; DLBCL: diffuse large B cell lymphoma; AlloSCT: allogeneic stem cell transplant; FL: follicular lymphoma;

Figure 1. Treatment schema

Comentado [IJ7]: Errata: Melpahalan

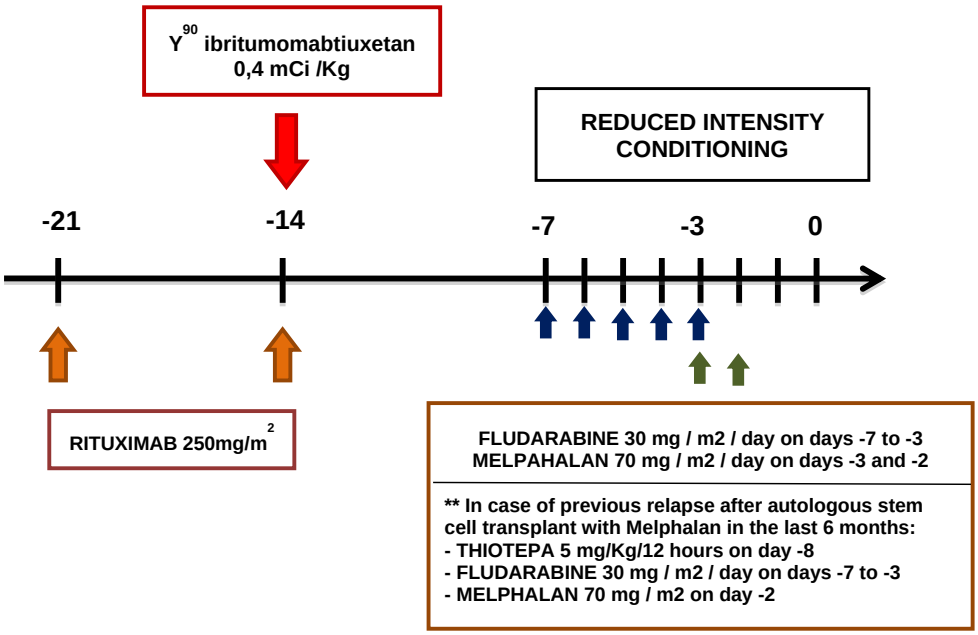
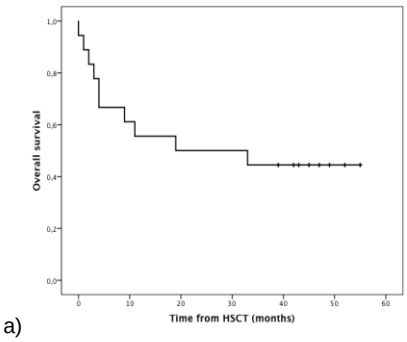
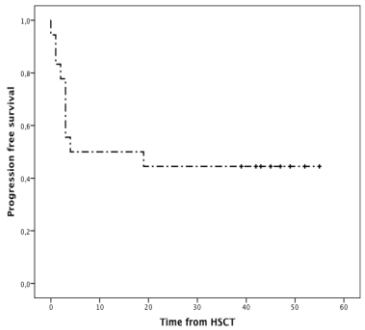


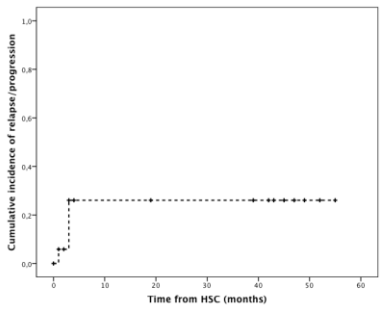
Figure 2: a) Overall survival (OS); b) Progression Free Survival (PFS); c) Cumulative Incidence of relapse; d) Transplant Related Mortality (TRM).



a)



b)



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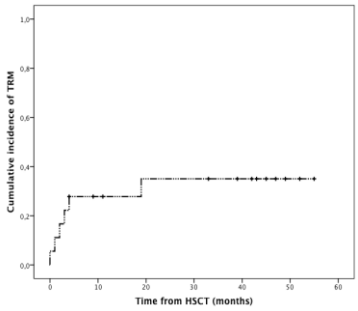
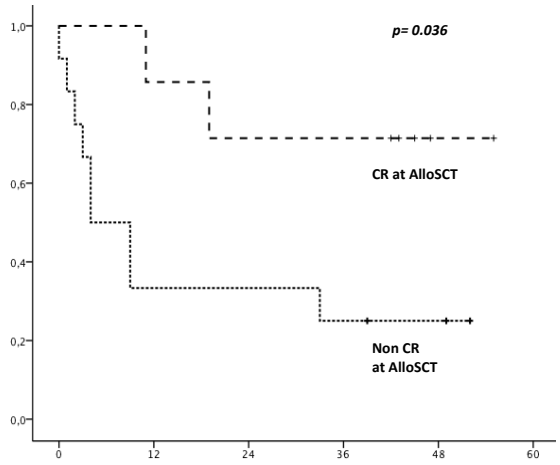


d)

Figure 3. a) OS depending on status at AlloSCT or **b)** acute graft versus host disease (aGVHD)

a)



b)