Allogeneic stem cell transplantation as part of front line therapy for Mantle Cell Lymphoma

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Introduction

Mantle cell lymphoma (MCL) is a rare and generally aggressive form of non-Hodgkin lymphoma. It is a disease that predominantly affects older individuals with a median age at presentation of around 70 years. At the point patients require therapy the use of rituximab together with chemotherapy is effective in the majority(Campo & Rule, 2014), however for many these responses are not durable and relapse is inevitable. For younger patients, the use of high dose cytarabine together with rituximab is currently considered as an induction therapy of choice. This can either be given as part of multi-agent chemotherapy with the Hyper-CVAD approach(Romaguera *et al*, 2010) or used with fewer additional agents and then consolidated with an autologous stem cell

transplant(Geisler *et al*, 2012). More recently the adoption of rituximab as maintenance therapy following an autograft has been shown to significantly improve progression free survival and overall survival(Le Gouill *et al*, 2017) These approaches deliver excellent long term remissions with 50% of patients alive at 10 years, but there is a continuing pattern of relapse with long term follow up and no suggestion that this approach is curative (Eskelund *et al*, 2016).

The use of allogeneic transplantation for the treatment of MCL has been reported since the late 1990s but the toxicity of conventional myeloablative regimens has limited its application. The development of reduced intensity conditioning (RIC) regimens has enabled allogeneic transplantation (alloSCT) to be used in older, less fit patients and thus applied more broadly in MCL. Several groups have previously reported the outcome of RIC alloSCT in patients with MCL (Le Gouill *et al*, 2012; Cook *et al*, 2010; Fenske *et al*, 2014; Maris *et al*, 2004; Robinson *et al*, 2018). These published series are generally small, include heterogeneous groups of patients and include patients that have failed a prior autologous SCT. However these studies have provided evidence of an allogeneic graft versus mantle cell lymphoma effect (Le Gouill *et al*, 2012; Cook *et al*, 2010) and durable long term remissions have been observed (Khouri *et al*, 2003; Vaughn *et al*, 2015). The efficacy and toxicity of a RIC alloSCT to consolidate first line therapy in MCL has only been reported in the context of retrospective studies. We therefore wished to test the use of RIC alloSCT as part of front line therapy for young patients with MCL in a prospective trial.

Methods

Study design

This trial (ClinicalTrials.gov identifier: NCT00720447) was a prospective study evaluating RIC alloSCT as consolidation therapy following initial treatment in patients with MCL, supported by the British Society of Blood and Marrow Transplantation (BSBMT) Clinical Trials Committee. The study was conducted according to the Declaration of Helsinki and relevant International Conference on Harmonisation Good Clinical Guidelines. It was approved by an independent ethics committee and had local approval from all participating sites. The trial was funded by Cancer Research UK (C7627/A9080) and trial management was performed by the Cancer Research United Kingdom and University College London Cancer Trials Centre.

Patients were required to have a confirmed diagnosis of MCL. There were no specific age restrictions but the responsible transplant physician was required to determine that the patient met local guidelines for fitness to proceed to a transplant procedure. In addition general inclusion criteria were as follows: Karnofsky score > 60%, creatinine clearance > 50ml/min, cardiac ejection fraction > 50%, the use of effective contraception, a negative pregnancy test for pre-menopausal women, no relevant co-morbidities and signed informed consent. Exclusion criteria included severe impairment of liver function (alkaline phosphatase >2 or serum bilirubin >1.5 times upper limit of normal) not related to lymphoma, or previous malignancy in the last 5 years (excluding non-melanoma skin tumour or curatively resected in situ carcinoma of the uterine cervix). In addition, patients

with a history of a psychological illness or condition that in the opinion of the investigator may adversely affect compliance were excluded.

Patients were required to have had a response to initial therapy, defined as at least a partial remission assessed by conventional response criteria(Cheson *et al*, 2007) (without the use of PET scanning). The choice of primary induction therapy was permissive and at the discretion of the individual physicians. Patients were enrolled into the trial following response assessment. RIC AlloSCT was performed using BEAM-Campath conditioning (BCNU 300 mg/m^2 on day -6, Etoposide 200 mg/m^2 od days -5 to -2, Ara-C 200 mg/m^2 bd days -5 to -2, Melphalan 140 mg/m^2 on day -1, and Campath IH 10 mg IV on days -5 to -1). The graft source was either a matched related family donor (MRD) or a 10/10 HLA_matched unrelated donor (MUD). Graft versus host disease (GVHD) prophylaxis was standardised, consisting of cyclosporine A (CsA), which was continued until day +30 and then weaned and stopped at between day +60 and +100 provided there was no GVHD. Methotrexate was not given. CsA could be withdrawn earlier if mixed chimerism was detected at day +30. Growth factors were started at day +7 and continued until engraftment. Anti-infective prophylaxis was given according to local standards.
Disease assessment and post-transplant chimerism studies were performed at protocol-defined time points and donor lymphocyte infusions given as per a standard protocol (see below).

Donor Lymphocyte Infusions (DLI)

DLI were administered in 3 settings; in patients with evidence of residual disease, patients experiencing disease progression, or in those with mixed chimerism. In patients with evidence of disease progression, DLI could be given from 3 months post-transplant at a dose of 1 x 10^7 CD3+ /kg for those with a MRD or 1 x 10^6 CD3+/kg for those with an MUD, and at 6 months post-transplant, at a dose of 1 x 10^8 CD3+/kg for those with a MRD and at 1 x 10^7 CD3+ /kg for those with an MUD. Patients with either low level clinical or molecular disease or mixed chimerism were eligible to receive an escalting dose schedule of DLI at 3 monthly intervals from 6 months post-transplant depending on their response and evidence of GVHD. Those with a MRD received 1 x 10^6 CD3+/kg, 2 x 10^6 CD3+/kg, 5 x 10^6 CD3+/kg and 1 x 10^7 CD3+/kg, whilst those with a MUD received a lower initial dose of 5 x 10^5 CD3+/kg, followed by 1 x 10^6 CD3+/kg, 2 x 10^6 CD3+/kg and 5 x 10^6 CD3+/kg. Patients were assessed for disease response and chimerism status 2 months after each dose of DLI. If complete remission (CR) or full donor chimerism was achieved no further DLI was administered.

Statistical methods

A Fleming single stage design was used to calculate the sample size. A minimum of 15/25 patients alive and progression free at 2 years were required to show an increase in 2 year PFS from 45% to 70% with a 10% alpha and 90% power. Survival endpoints are measured from the date of transplant until the event or date last seen for censored patients. All analyses were performed in Stata version 15.1 [StataCorp, Texas].

Results

Patient Characteristics

Twenty-five patients were recruited between January 2010 and September 2013 from 8 transplant centres in the United Kingdom. The baseline characteristics are described in Table 1. The median age was 54 (range 34-70) and 88% of patients were male. MIPI scores were available for 23 patients of which 15 (65%) were low and 4 (17%) were intermediate. At the time of transplant 11 (44%) were in a CR and 14 (56%) in a partial remission (PR). A range of different chemotherapies were used to achieve remission, the vast majority (n=17, 68%) of which included cytarabine and all but 5 patients received rituximab as part of initial therapy. Two patients received more than 1 chemotherapy line prior to transplant as they had experienced progression through initial therapy.

Engraftment and chimerism

Eleven (44%) patients received a graft from an MRD, and 14 from an MUD. No mismatched grafts were used. One patient failed to engraft (4%) but was successfully transplanted, using the same donor, following fludarabine, busulphan and ATG conditioning. Of the other 24 patients, all had neutrophil and platelet recovery by day 100 post-transplant (neutrophils above $0.5x10^9$/L and platelets over $20x10^9$/L) with a median time to neutrophil and platelet engraftment of 12 days (range 9-104 days) and 11 days (range 8-104) respectively. Of the 24 patients that engrafted after the BEAM-CAMPATH conditioning, chimerism analysis on whole blood cells revealed that 20 achieved full donor chimerism at some point post-transplant, 2 remained mixed donor-

recipient and two patients died prior to evaluation. Of 8 patients given DLI for mixed chimerism, 6 became fully donor after a median of 3 DLIs (1-6) and 2 did not respond. At the last chimerism evaluation (median 23.7 months (3.4 – 67.4)), 3 more patients had become donor-recipient mixed chimeras leaving 17 fully donor. GVHD developed in 3 patients (2 extensive chronic GVHD, 1 limited chronic GVHD) following administration of DLI.

Toxicity, GVHD and NRM.

Acute toxicities were as expected (Table 2); all patients experienced at least 1 grade 3/4 adverse event with the most common non-haematological events being infection (50% grade 3/4) and mucositis (25% grade 3/4). There were no non-relapse mortality events before day 100 but there were three later events (2 sepsis (6.6 and 11.9 months), 1 car accident) resulting in a 2 year non-relapse mortality (NRM) rate of 13% (95% CI: 4.4-35.2%). Of the 24 patients who engrafted, GVHD was reported in 14 (58%) patients. Nine (38%) experienced acute (7 grade I and 2 grade II) and 14 (58%) chronic GVHD (6 limited and 8 extensive) with a cumulative incidence of chronic GVHD at 1 year of 50.3% (95% CI: 29.1-68.2%).

Disease Relapse/Progression

The disease status at 100 days post-transplant was CR in 15, alive without progression in 8 and relapse/progression in 2. Disease relapse/progression occurred in 9 patients. The cumulative incidence of relapse at 2 years was 21% (95% CI 9.3% – 43.5%) (Figure

1). Disease relapse was treated with a variety of different strategies at the discretion of the treating physician.

Progression free and overall survival

With a median follow up of 60.5 months (6.5 – 97.1) there have been 12 PFS events including 6 deaths (3 from MCL, 3 NRM). The trial met its primary endpoint with 17 patients alive and progression free at 2 years. The median PFS is 68.8 months and K-M estimates for PFS and OS were 68.0% (46.1 – 82.5) and 80% (95% CI 58.4-91.2%) at 2 years and 56.0% (34.8 – 72.7) and 75.8% (53.8 – 88.3) at 5 years (Figure 2). PFS was very similar for both sibling and unrelated transplants and there was no difference in PFS between patients in PR or CR prior to transplant (Figure 3).

Discussion

Allogeneic transplantation for MCL is currently considered as a treatment option for younger patients with relapsed disease and no preclusive comorbidities (ESMO, BSH and EBMT guidelines), (Dreyling *et al.* 2014; McKay *et al*. 2018; Robinson *et al*, 2015). There have been multiple published series of patients with MCL undergoing an allogeneic transplant in this setting with a range of treatment outcomes(Le Gouill *et al*, 2012; Vaughn *et al*, 2015; Robinson *et al*, 2015). These studies demonstrate that a proportion of patients achieve prolonged disease free survival and probable cure. Together with reports documenting disease response to DLI in those with disease relapse following transplantation(Cook *et al*, 2010), these studies indicate the existence of a clinically

relevant graft versus lymphoma effect. The application of less toxic RIC allogeneic procedures has allowed further evaluation of allogeneic transplantation, although most experience remains restricted to those with relapsed disease. The largest experience of use to consolidate primary induction therapy comes from an analysis of patients on the Centre for International Blood and Marrow Research (CIBMTR) database who received either an autologous or RIC alloSCT for chemotherapy sensitive MCL (Fenske *et al*, 2014) Patients were analysed by time of transplantation into early (in first PR/CR after no more than 2 lines of prior therapy) or late (all other patients), and the 'early' cohort included 50 patients receiving RIC allografts. For early transplantation, relapse was significantly lower in favour of RIC alloSCT (15% versus 32% at 5 years), supporting a graft versus lymphoma effect, but overall survival was indistinguishable (62% versus 61%) due to a higher non-relapse related mortality in the patients receiving a RIC alloSCT. Further follow-up is required to determine whether there are any longer term benefits in the alloSCT group as both progression free and overall survival curves crossed at between 4-5 years post-transplant.

There has been only one previous prospective study evaluating RIC alloSCT as part of front line therapy. The final report of the East German Study Group of Haematology and Oncology (OSHO)(Krüger *et al*, 2014) combined data on two studies, one frontline and the other in relapsed patients. In the front-line study 21 patients proceeded to an allogeneic procedure following either R-CHOP or R-CHOP/R-DHAP induction therapy. Transplant outcomes are reported as a combined figure for patients on both studies, though it is noted that the outcomes appeared the same whether the transplant was

performed up front or at relapse and the remission status bore no relationship to outcome. At transplant only 43% were in a complete remission but at 5 years the overall survival was 73%.

The current study extends this limited experience of alloSCT in front-line consolidation. Twenty-five patients were transplanted as consolidation following a variety of chemotherapy induction regimens. A similar proportion (44%) of the patients were in a CR at time of the transplant as in the German study and, likewise, remission status pre-transplant did not influence overall survival outcomes. Excluding the car accident, the 2-year non relapse related mortality was only 8.9 with a corresponding PFS and OS of 68% and 80% respectively. The observed NRM is low considering that this is a multi-centre study and may reflect the fact that patients had not been exposed to significant prior therapies with the attendant toxicities. Chronic GVHD was observed in 58% patients, which has an impact on quality of life and the requirement for on-going therapy, although it was limited in just under half of these. These data are therefore consistent with the OSHO experience. Whilst immature, the outcomes observed here are encouraging. They must, however, be balanced against the excellent intermediate term outcomes for young patients following cytarabine based therapy with autologous transplantation as consolidation. In these patients long term toxicity is significantly lower, and subsequent salvage in relapsing patients and RIC alloSCT may offer the optimal overall management strategy. As such all of the major guidelines retain the allogeneic approach as one of the options in the relapse setting.

One question that arises is whether cohorts of higher risk patients could be identified that might benefit more from earlier alloSCT. A recently published paper from the Nordic lymphoma group (Eskelund *et al*, 2017) looked at long term follow up of 183 younger patients treated within their up front autologous stem cell trials (NORDIC 2 and 3). Whilst there were a number of factors that identified for an inferior outcome in univariate analysis, on multivariate analyses only TP53 mutation retained a prognostic impact with respect to overall survival. In this group (11% of the patients) 50% relapsed within 1 year and the overall survival was only 1.8 years. In this group it would appear reasonable to consider exploration of alternative treatment approaches that could include front line alloSCT. There are a number of exciting novel agents that could have a role here, most notably the BTK inhibitors (Wang *et al*, 2013, 2017) although longer term outcomes remain unknown with these agents as is the response in patients with MCL harbouring TP53 mutations. Our study did not look specifically at these high risk patients but the feasibility of our approach and the extremely poor outcomes seen with young patients harbouring a TP53 mutation suggests a follow up study for this group is warranted.

In summary, front line alloSCT as used to consolidate initial therapy is associated with a low TRM and good OS. However, there is an on-going pattern of relapse and longer follow up will be important to see how durable these remissions are. With the excellent results seen with the front line autologous stem cell based therapies our results do not challenge the current guidelines with alloSCT reserved for treatment after relapse. However a strong argument can be made for using this approach in young patients with a TP53 mutation who's outcome is extremely poor with conventional approaches.

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Author contributions

SR designed the study, interpreted the data and wrote the manuscript. GC,NR,SR,AK,KP designed the study, interpreted data and critically revised the manuscript. AH,NM,AS,PP,LC,TA participated in data analysis and critically revised the manuscript. All authors gave their consent for the final version of the manuscript.

Author Conflicts of Interest

The authors declare no conflicts of interest

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Table 1: Baseline characteristics

		N (%)
Sex		
Male		22 (88.0)
Female		3 (12.0)
Age at transplant, median (range)	54 (34-70)	
ECOG at Diagnosis		
0		12 (48.0)
1		13 (52.0)
Stage At Diagnosis		
I		1 (4.0)
III		5 (20.0)
IV		19 (76.0)
Bulky disease		
Absent		18 (72.0)
Present		7 (28.0)

Response to induction chemo	
CR	11 (44.0)
PR	14 (56.0)
MIPI	
Low risk	15 (65.2)
Intermediate risk	4 (17.4)
High risk	4 (17.4)
Missing	2
Time from diagnosis to SCT, median (range)	274 days (98 – 485)
Donor matching	
Matched sibling	11 (44.0)
MUD	14 (56.0)

Table 2: Adverse events*

System organ class/Event Term	Worst grade Grade 3+ N(%)
Allergy/Immunology	**2 (8.33)**
Allergy/Anaphylaxis	2 (8.33)
Blood/Bone Marrow	**24 (100.00)**
Haemoglobin	6 (25.00)
Neutrophils	24 (100.00)
Platelets	8 (33.33)
Cardiac General	**1 (4.17)**
Hypotension	1 (4.17)
Constitutional Symptoms	**7 (29.17)**
Fatigue	2 (8.33)
Fever	4 (16.67)
Weight Loss	1 (4.17)
Gastrointestinal	**8 (33.33)**
Anorexia	4 (16.67)
Diarrhoea	4 (16.67)
Heartburn	1 (4.17)
Nausea	3 (12.50)
Other - Dilated Small & Large Bowel	1 (4.17)
Haemorrhage/Bleeding	**1 (4.17)**
Haemorrhage	1 (4.17)
Infection	**12 (50.00)**
Infection - Fungal	2 (8.33)
Infection - Neutropenic Sepsis	10 (41.67)
Infection With Neutropenia	1 (4.17)
Infection Without Neutropenia	1 (4.17)
Infection With Unknown ANC	1 (4.17)
Opportunistic Infection (CMV)	1 (4.17)
Metabolic/Laboratory	**2 (8.33)**
Potassium - Serum Low	2 (8.33)
Non CTC AE	**6 (25.00)**
Mucositis	6 (25.00)
Pain	**2 (8.33)**
Pain - Dermatology - Tooth/Gum	1 (4.17)
Pain - Stomach	1 (4.17)
Any toxicity	**24 (100.00)**

*AE data was not reported for the patient who failed to engraft and was given a second SCT soon after.

Figure 1. Time to relapse

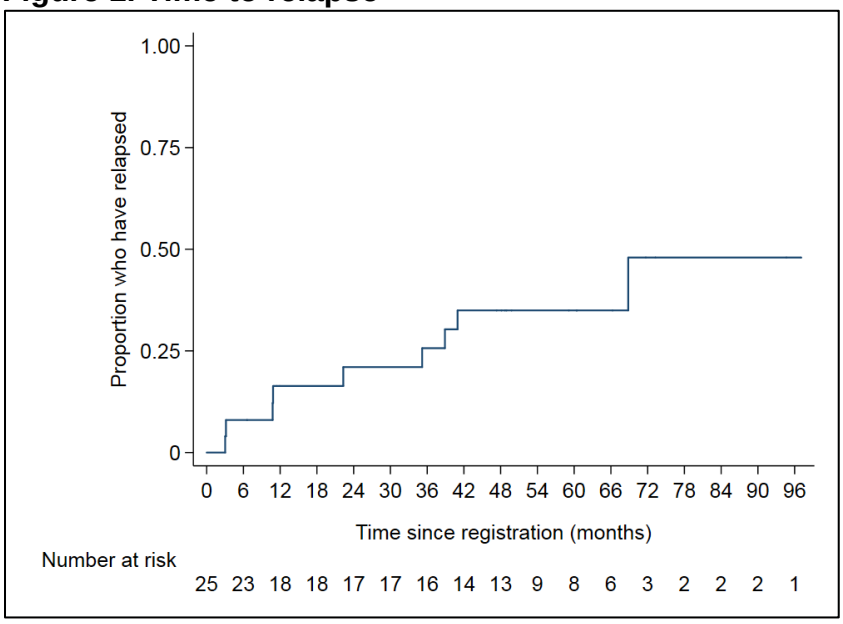
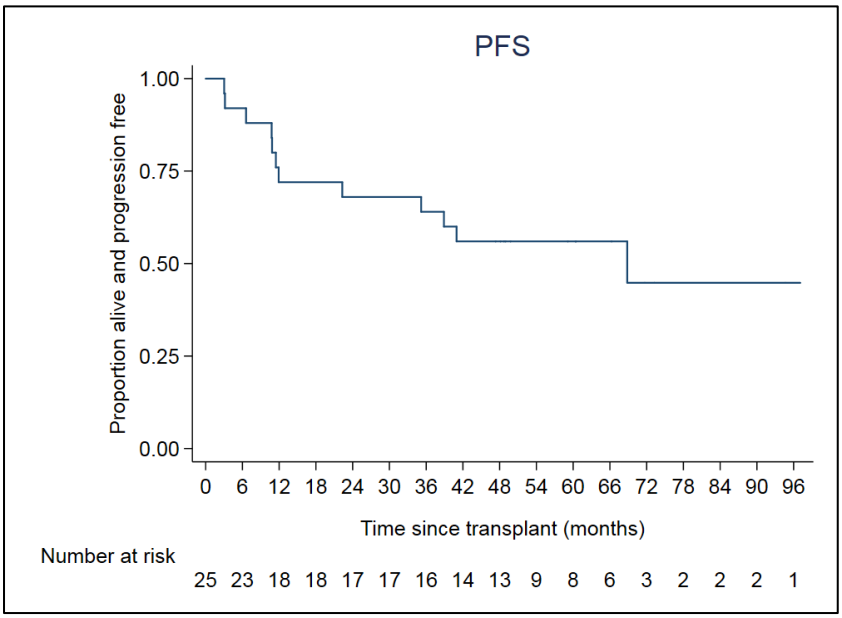


Figure 2. Progression free and Overall survival

a. PFS



b. OS

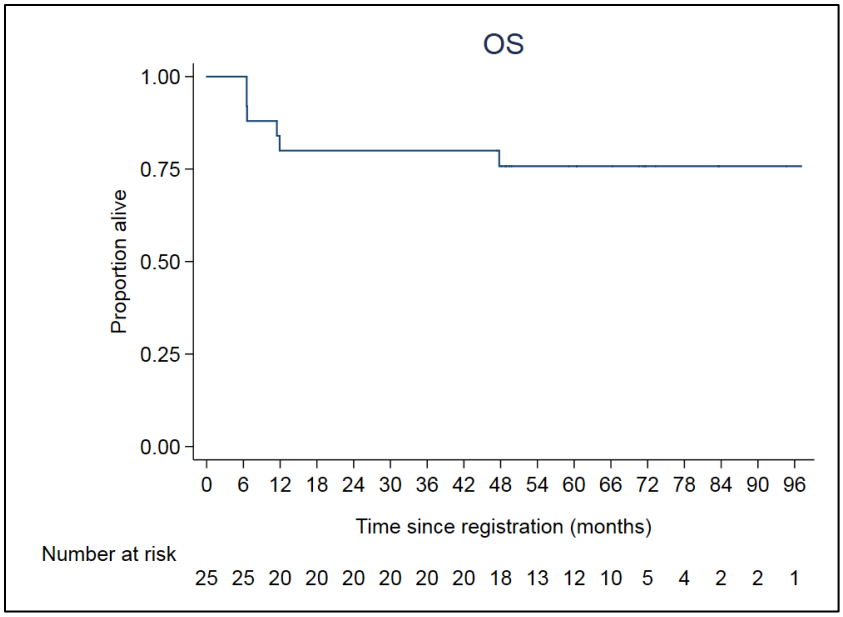
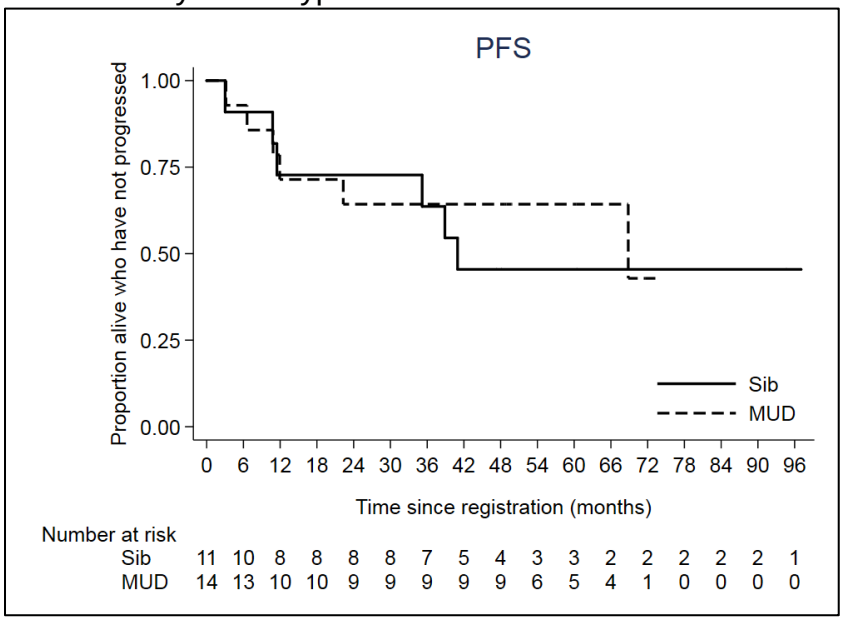


Figure 3. Progression free survival by subgroup

a. By donor type



b. By remission status prior to transplant