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## The Addition of Sirolimus to the Graft-Versus-Host Disease Prophylaxis Regimen in Reduced Intensity Allogeneic Stem Cell Transplantation for Lymphoma: A Multicentre Randomized Trial

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### AUTHOR CONTRIBUTIONS

P.A. designed the research, analysed the data and wrote the paper.

H.T.K. designed the research, analysed the data and edited the paper.

M.M.S. collected data and edited the paper.

P.B.L. collected data and edited the paper.

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### CONFLICT OF INTEREST DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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## Abstract

Inhibition of the mechanistic target of rapamycin (serine/threonine kinase) (mTOR) pathway has clinical activity in lymphoma. The mTOR inhibitor sirolimus has been used in the prevention and treatment of graft-versus-host disease (GVHD) after allogeneic haematopoietic stem cell transplantation (HSCT). A retrospective study suggested that patients with lymphoma undergoing reduced intensity conditioning (RIC) HSCT who received sirolimus as part of their GVHD prophylaxis regimen had a lower rate of relapse. We therefore performed a multicentre randomized trial comparing tacrolimus, sirolimus and methotrexate to standard regimens in adult patients undergoing RIC HSCT for lymphoma in order to assess the possible benefit of sirolimus on HSCT outcome. 139 patients were randomized. There was no difference overall in 2-year overall survival, progression-free survival, relapse, non-relapse mortality or chronic GVHD. However, the sirolimus-containing arm had a significantly lower incidence of grade II-i.v. acute GVHD (9% versus 25%,  $p=0.015$ ), which was more marked for unrelated donor grafts. In conclusion, the addition of sirolimus for GVHD prophylaxis in RIC HSCT is associated with no increased overall toxicity and a lower risk of acute GVHD, although it does not improve survival; this regimen is an acceptable option for GVHD prevention in RIC HSCT. This trial is registered at [clinicaltrials.gov](http://clinicaltrials.gov) (NCT00928018).

## Keywords

clinical trials; lymphomas; stem cell transplantation; GVHD

## INTRODUCTION

The mTOR [mechanistic target of rapamycin (serine/threonine kinase)] inhibitor sirolimus has been used extensively for the prevention and treatment of graft-versus-host disease (GVHD) after allogeneic haematopoietic stem cell transplantation (HSCT) (Alyea, *et al* 2008, Antin, *et al* 2003, Benito, *et al* 2001, Couriel, *et al* 2005, Cutler, *et al* 2004, Cutler, *et al* 2007, Furlong, *et al* 2008, Ho, *et al* 2009, Johnston, *et al* 2005, Jurado, *et al* 2007, Perez-Simon, *et al* 2013, Rodriguez, *et al* 2010, Rosenbeck, *et al* 2011). A randomized phase II trial in patients receiving mostly myeloablative HSCT suggested a benefit to tacrolimus/sirolimus (Tac/Sir) over tacrolimus/methotrexate (Tax/Mtx) (Pidala, *et al* 2012) in terms of acute GVHD prevention; however, a phase III randomized trial (Blood and Marrow Transplantation Clinical Trial Network [BMT CTN] 0402) comparing those 2 regimens in patients undergoing myeloablative HSCT from matched related donors for acute myeloid leukaemia, myelodysplastic syndromes or acute lymphoblastic leukaemia (ALL) showed no significant difference in acute GVHD (aGVHD)-free survival (Cutler, *et al* 2012), despite a trend towards lower rates of aGVHD. Of note, this trial did not enrol patients receiving unrelated donor grafts, who are at higher risk of aGVHD, and methotrexate was omitted from the experimental arm. Another randomized trial (Children's Oncology Group [COG] ASCT0431) showed that sirolimus, when added to tacrolimus and methotrexate, reduced the risk of grade II-i.v. acute GVHD in children with ALL receiving a myeloablative HSCT

from related, unrelated or cord blood donors, but at the expense of an increase in veno-occlusive disease (VOD) and thrombotic microangiopathy (TMA)(Pulsipher, *et al* 2014). A more recent randomized phase 2 study in patients receiving reduced intensity conditioning (RIC) HSCT from unrelated donors suggested a decrease in acute GVHD when sirolimus was added to tacrolimus and mycophenolate mofetil (Kornblit, *et al* 2014). In parallel, other mTOR inhibitors (everolimus and temsirolimus) have demonstrated clinical activity in a variety of lymphoma histologies, including non-Hodgkin and Hodgkin lymphoma (NHL and HL)(Ansell, *et al* 2008, Ansell, *et al* 2011, Barnes, *et al* 2013, Ghobrial, *et al* 2010, Hess, *et al* 2009, Renner, *et al* 2012, Witzig, *et al* 2005, Witzig, *et al* 2011). We previously conducted a retrospective study at our institution which suggested that patients with lymphoma who received a sirolimus-containing GVHD prophylaxis regimen had a lower risk of relapse and a lower risk of grade II-i.v. aGVHD(Armand, *et al* 2008); in this study the relapse benefit was only apparent in patients who received a reduced intensity conditioning (RIC) HSCT. A subsequent report also suggested favourable outcomes in patients with lymphoid malignancies receiving this regimen(Ceberio, *et al* 2015). Therefore, we prospectively tested the putative benefit of the addition of sirolimus to the GVHD prophylaxis regimen in a multicentre randomized clinical trial in patients with lymphoma undergoing RIC HSCT; this is the first phase III randomized trial of sirolimus in RIC transplantation, and the first phase III trial to test the addition of sirolimus to methotrexate rather than the replacement of methotrexate by sirolimus.

## METHODS

### Patients and Centres

This phase III, open-label, randomized clinical trial enrolled patients at 5 transplant centres in the United States. Eligible participants were adults aged 18-72 years with any lymphoma type, including HL and B- or T-cell NHL, with the exception of Burkitt lymphoma or diffuse large B cell lymphoma (DLBCL) known to harbour a *MYC* translocation. Patients had to have a matched (8/8) related (MRD) or unrelated (MUD) donor. Exclusion criteria included prior allogeneic HSCT, Karnofsky performance status (KPS)  $\geq$  70%, uncontrolled infection, creatinine  $\geq$  176.8  $\mu$ mol/l, total bilirubin  $\geq$  34.2  $\mu$ mol/l, alanine aminotransferase or aspartate aminotransferase  $\geq$  3 times upper limit of normal, left ventricular ejection fraction  $<$  30%, cholesterol  $>$  12.95 mmol/l or triglycerides  $>$  5.65 mmol/l despite appropriate treatment, and seropositivity for i.v.human immunodeficiency virus. All patients signed informed consent; the study was registered on clinicaltrials.gov (NCT00928018), monitored by an independent Data and Safety Monitoring Board (DSMB), and conducted in accordance with the principles of the Declaration of Helsinki. Patients were enrolled between June 2009 and November 2012.

### Transplantation

Because of the multicentre nature of this study, each centre could select at the outset one of two conditioning regimens. All centres except one used Flu/Bu (fludarabine 30 mg/m<sup>2</sup> i.v. + busulfan 0.8 mg/kg i.v. daily given on days -5 to -2); patients transplanted at the University of Minnesota (UMN) received their standard RIC regimen of Flu/Cy/TBI (fludarabine 30 mg/m<sup>2</sup> i.v. on days -6 to -2, cyclophosphamide 50 mg/kg i.v. on day -6, and total body

irradiation in a single 200 cGy fraction on day -1). All patients received filgrastim-mobilized peripheral blood (PB) grafts at a target dose of  $2-10 \times 10^6$  CD34+ cells/kg recipient weight. Supportive care was given per institutional guidelines.

### GVHD Prophylaxis

Patients were randomized 0-5 days prior to the start of conditioning to the experimental arm (Arm A) or the control arm (Arm B). Randomization was 1:1 and stratified by general histological group, centre and donor type, using a permuted block algorithm within strata. All patients on Arm A received tacrolimus (0.05 mg/kg orally b.i.d. starting day -3, with a goal trough level of 5-10 ng/ml), sirolimus (12 mg orally on day -3, then 4 mg daily, with a goal trough level of 5-12 ng/ml) and low-dose methotrexate (5 mg/m<sup>2</sup> i.v. days 1, 3, and 6) (Tac/Sir/Mtx). Each centre could select one of two control GVHD prophylaxis regimens. All centres except one used tacrolimus (with the same dose and trough goal as on Arm A) + low-dose methotrexate (as on Arm A with an extra dose on day 11 for recipients of an unrelated donor graft) (Tac/Mtx, Arm B1). Patients transplanted at UMN received their standard RIC GVHD regimen of ciclosporin (6 mg/kg b.i.d. starting day -3, with a goal trough level of 200-400 ng/ml) + mycophenolate mofetil (3 g daily orally in 2-3 divided doses, starting on day 3) (CSA/MMF, Arm B2). Tapering was at the discretion of the treating clinician, but the study recommended that the calcineurin inhibitor be tapered between days 100 and 180, sirolimus between days 180 and 360, and MMF (for patients on Arm B2) stopped at day 30.

### Statistical Analysis

Baseline characteristics were compared between the two arms using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables. The primary endpoint of the study was 2-year overall survival (OS), defined as the time from randomization to death from any cause. Secondary endpoints included toxicity, progression-free survival at 2 years (PFS), defined as the time from randomization to disease relapse, progression or death from any cause, whichever occurred first, cumulative incidence of relapse/progression (CIR) and non-relapse mortality (NRM), 6-month cumulative incidence of grade II-IV and grade III-IV aGVHD, and 2-year cumulative incidence of chronic GVHD (cGVHD). GVHD was defined according to standard criteria (Przepiorka, *et al* 1995). Other endpoints included a comparison of arm A with arm B1 (Tac/Mtx), and comparisons of outcomes within each broad histological group (indolent B-cell NHL, aggressive B-NHL including mantle cell lymphoma [MCL], T-cell NHL and HL). The study was powered to detect a 20% difference in 2-year OS between the 2 arms, based on the results of our retrospective study (Armand, *et al* 2008). With 136 eligible patients, the study had 81% power at a one-sided significance level of 0.025. Because patients would be randomized within the 5 days preceding the beginning of conditioning, in order to account for the possibility that a randomized patient might not actually proceed to transplantation, the accrual goal was set to 140. Two interim analyses were planned with stopping rules in favour of the alternative hypothesis using truncated O'Brien-Fleming boundaries (Freidlin, *et al* 1999), and with stopping rule for futility using repeated confidence interval (RCI) methodology similar to that described by Jennison and Turnbull (1984). The primary analysis was an intention-to-treat analysis with all randomized patients. OS and PFS were

calculated using the Kaplan-Meier method, and the stratified log-rank test was used for comparisons of the arms. CIR, NRM and GVHD were calculated in the competing risks framework and compared using Gray test (Gray 1988). Cox proportional hazards model was used for multivariate analyses. All calculations were performed using SAS 9.3 (SAS Institute Inc, Cary, NC), and R version 2.13 (R Foundation for Statistical Computing, Vienna Austria).

## RESULTS

### Patients

A total of 140 patients were randomized; 67 to Arm A and 73 to Arm B. One patient was registered and randomized to Arm A, but had transplantation delayed because of liver dysfunction. He was later re-registered and randomized on Arm B, and analysed as such. Therefore, 139 individual patients were treated and analysed. One patient randomized to Arm A withdrew consent for treatment and was treated as on Arm B, but analysed in Arm A based on intent-to-treat. Therefore, 65 of the 67 patients on Arm A received treatment per protocol, as did all 73 patients on Arm B (69 on Arm B1 and 4 on Arm B2). One hundred and thirty-two patients received Flu/Bu conditioning, while the remaining 7 received Flu/Cy/TBI. Patient characteristics are shown in Table I. Median age was 57 (range, 23-70) years; 88% were transplanted with chemosensitive disease; 47% had previously received an autologous stem cell transplant; 40% received a graft from an MRD and 60% from a MUD.

### Toxicity

Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)). The study required reporting of all grade 2 adverse events (AEs) that were unexpected and related to study treatment, as well as any grade 3 or above event whether related or not. Given the difficulty of attributing AEs on this study, since any infectious or GVHD-related toxicity could be attributed to the GVHD prophylaxis regimen, we considered and compared all AEs regardless of attribution. As shown in Table II, there was no excess grade 3 or 4 toxicity in the experimental arm. In fact, the number of grade 3-4 events was lower on Arm A than on Arm B (128 versus 194). There was no reported VOD on either arm. There was no excess risk of severe myelosuppression or hyperlipidaemia on Arm A; there was as expected an increased risk of grade 3-4 TMA, with 15 events (including events reported as renal failure or haemolysis) versus 8 on Arm B (4 versus 2 for grade 4 events); conversely, the number of grade 3-4 infections was lower in Arm A (9 versus 18).

### Graft-versus-host disease

As shown in Figure 1A, the 6-month cumulative incidence of grade II-IV aGVHD on Arm A was 9% (95% confidence interval [95CI] 4-18), which was significantly lower than on Arm B (25%, 95CI 15-35,  $p=0.015$ ). There was no difference in grade III-IV aGVHD (3% versus 4%,  $p=0.7$ , Figure 1B), or in the 2-year incidence of cGVHD (59% versus 63%,  $p=0.5$ , Figure 1D). The difference in aGVHD was similar in a comparison of Arm A with Arm B1 (Tac/Mtx group; not shown). In additional analyses not pre-specified per protocol,

we compared the incidence of aGVHD among patients receiving MRD grafts (4% on Arm A versus 14% on Arm B,  $p=0.2$ ) and among those receiving MUD grafts (13% versus 32%,  $p=0.038$ ) (Figure 1C). We also compared incidences of aGVHD using the International Bone Marrow Transplant Registry grading (Rowlings, *et al* 1997); the incidence of grade B-D aGVHD was 12% on Arm A versus 34% on Arm B ( $p=0.002$ ); that of grade C-D was 8% versus 16% ( $p=0.11$ ). We also analysed *post hoc* the differences in aGVHD by organ involved, for exploratory purposes, and found that the difference in aGVHD was significant only for skin and for liver disease, but not for gut disease. For cGVHD, there was no difference between arms for either MRD or MUD groups, and no difference in extensive disease (not shown). The proportion of patients who received systemic corticosteroids in the first year after HSCT was 47% on Arm A versus 60% on Arm B ( $p=0.13$ ).

## Survival

There was no difference between the study arms in OS, PFS, CIR or NRM (Figure 2). The 2-year OS was 70% (95CI 57-79) on Arm A versus 68% (95CI 57-78) on Arm B ( $p=0.7$ ). The 2-year PFS was 61% (95CI 48-71) versus 58% (95CI 45-68) ( $p=0.9$ ); the 2-year CIR 26% (95CI 16-37) versus 30% (95CI 20-41) ( $p=0.6$ ); and the 2-year NRM 14% (95CI 7-23) versus 12% (95CI 6-21) ( $p=0.6$ ). We also examined, in protocol-specified analyses, the impact of GVHD prophylaxis on OS and PFS within each histological subgroup. Given the small number of patients within each group, we considered indolent histologies (indolent B-cell NHL, chronic lymphocytic leukaemia and HL) together in one group (indolent group), and aggressive histologies (aggressive B-cell NHL, MCL and T-cell NHL) in another (aggressive group). Within the indolent group, the 2-year OS on Arm A was 82% versus 63% on arm B ( $p=0.082$ ) (Figure 2E); the corresponding PFS were 71% and 53%, respectively ( $p=0.13$ ). Within the aggressive group, the 2-year OS on Arm A was 54% versus 76% on arm B ( $p=0.077$ ) (Figure 2F); the corresponding PFS were 46% and 64%, respectively ( $p=0.24$ ). Based on this apparent difference, and since the 2 subgroups remained heterogeneous with respect to disease and patient risk, we conducted *ad hoc* multivariate analyses within each subgroup, including treatment assignment (arm A versus arm B), disease status at HSCT (complete remission [CR] versus partial remission [PR] versus advanced), age (< versus  $\geq 60$  years) and donor type (MRD versus MUD). In those models, the hazard ratio (HR) for mortality associated with Arm A (versus Arm B) in the indolent group was 0.4 (95CI 0.2-1.0,  $p=0.056$ ), and in the aggressive group it was 2.3 (95CI 0.9-5.7,  $p=0.075$ ); the corresponding HRs for PFS were 0.5 (95CI 0.2-1.1,  $p=0.096$ ) in the indolent group and 1.7 (95CI 0.8-3.8,  $p=0.17$ ) in the aggressive group. The effect of sirolimus on acute and chronic GVHD incidences was similar in the indolent and the aggressive groups. In the indolent group, the 2-year CIR was 21% on Arm A and 33% on Arm B ( $p=0.4$ ), while 2-year NRM was 8% and 15% ( $p=0.5$ ), respectively; in the aggressive group, the 2-year CIR was 32% on Arm A and 27% on Arm B ( $p=0.9$ ), and NRM 21% and 9% ( $p=0.2$ ) respectively.

## DISCUSSION

The hypothesis for this trial was that the mTOR inhibitor sirolimus could exert a double benefit after HSCT: reduce the incidence of acute GVHD and the risk of lymphoma relapse.

However, the trial showed no evidence of a benefit for relapse prevention overall, in contrast to our previous retrospective study (Armand, *et al* 2008). It is possible that the decreased risk of relapse in the retrospective study was related to unmeasured confounders, especially as many patients in the sirolimus group had been treated in later years and often on clinical trials, both of which have been associated with improved outcomes (Armand, *et al* 2012, Gooley, *et al* 2010). However, it is also possible that the benefit of sirolimus on relapse prevention is histology-specific. In fact, there was a strong trend for an improvement in OS with sirolimus addition in patients with indolent histologies. Conversely, for patients with aggressive histologies, the addition of sirolimus appeared to be associated with a trend to a worse OS, which did not appear to be related to a differential effect on GVHD incidence. In the indolent group, there was a trend towards a lower relapse risk, but there was no such trend in the aggressive group. In general, mTOR inhibitors have shown therapeutic activity across both indolent and aggressive lymphoma histologies, so we cannot explain this finding based on our present understanding.

This trial did demonstrate a significant reduction in grade 2-4 aGVHD with the addition of sirolimus, which was a secondary endpoint. This benefit in terms of aGVHD prevention with the addition of sirolimus was apparent even when considering only arm A versus arm B1, a pre-specified comparison in which all patients received the same conditioning regimen (Bu/Flu) and the same GVHD prophylaxis backbone regimen (Tac/Mtx), with the only difference being the addition of sirolimus in the experimental arm (Arm A). There was no difference in the rates of severe aGVHD, which were very low in both arms. This finding of a protective effect with sirolimus on aGVHD incidence should be broadly applicable to RIC HSCT, as there is no reason to believe or evidence to suggest that GVHD rates are different for patients with lymphoma than they are for patients with other haematological malignancies. Naturally, this benefit may only be extrapolated to T-cell-replete peripheral blood RIC HSCT. This stands in contrast to the results observed on BMT CTN 0402 (Cutler, *et al* 2012). Differences between these two randomized trials may be related to three factors: first, CTN 0402 only enrolled patients with MRDs; in the present trial, it is apparent that the absolute benefit of sirolimus for aGVHD prevention is greater for MUDs (although there was a trend towards benefit even in the MRD cohort, which may have reached significance with a larger sample size); second, CTN 0402 tested the *substitution* of sirolimus for methotrexate, whereas the present study tested the *addition* of sirolimus to a methotrexate-containing regimen; third, this was a trial in the RIC setting while CTN 0402 was performed in the myeloablative setting. Our results regarding aGVHD are very similar to those of the COG ASCT0431 trial, which had nearly identical GVHD prophylaxis regimens on both the experimental and control arms as those on the present trial (Pulsipher, *et al* 2014). In that study, the benefit of sirolimus for aGVHD control was offset by an increase in VOD; this difference between the arms was not observed on our study, probably because VOD is extremely rare in the RIC setting. Therefore, the aGVHD benefit may be achieved in RIC HSCT without an overall increase in other severe toxicities. Indeed, while there was an excess of grade 3-4 TMA-related toxicity with sirolimus on our study, the overall grade 3-4 toxicity was lower on the sirolimus arm; we hypothesize that this reflects the less frequent use of systemic corticosteroids in the sirolimus arm, consistent with the lower incidence of acute GVHD. Patients in both arms still suffered from a ~60% incidence of chronic GVHD,



which demands further research on newer regimens that may decrease this risk without elevating the risk of relapse. This trial did not use the consensus criteria for diagnosing and grading chronic GVHD (Filipovich, *et al* 2005). It is possible, though unlikely, that the incidence of cGVHD would be different with those criteria. Together, our findings suggest that Tac/Sir/Mtx is an acceptable regimen with T-cell-replete RIC HSCT, with no overall excess toxicity and a lower risk of non-severe aGVHD.

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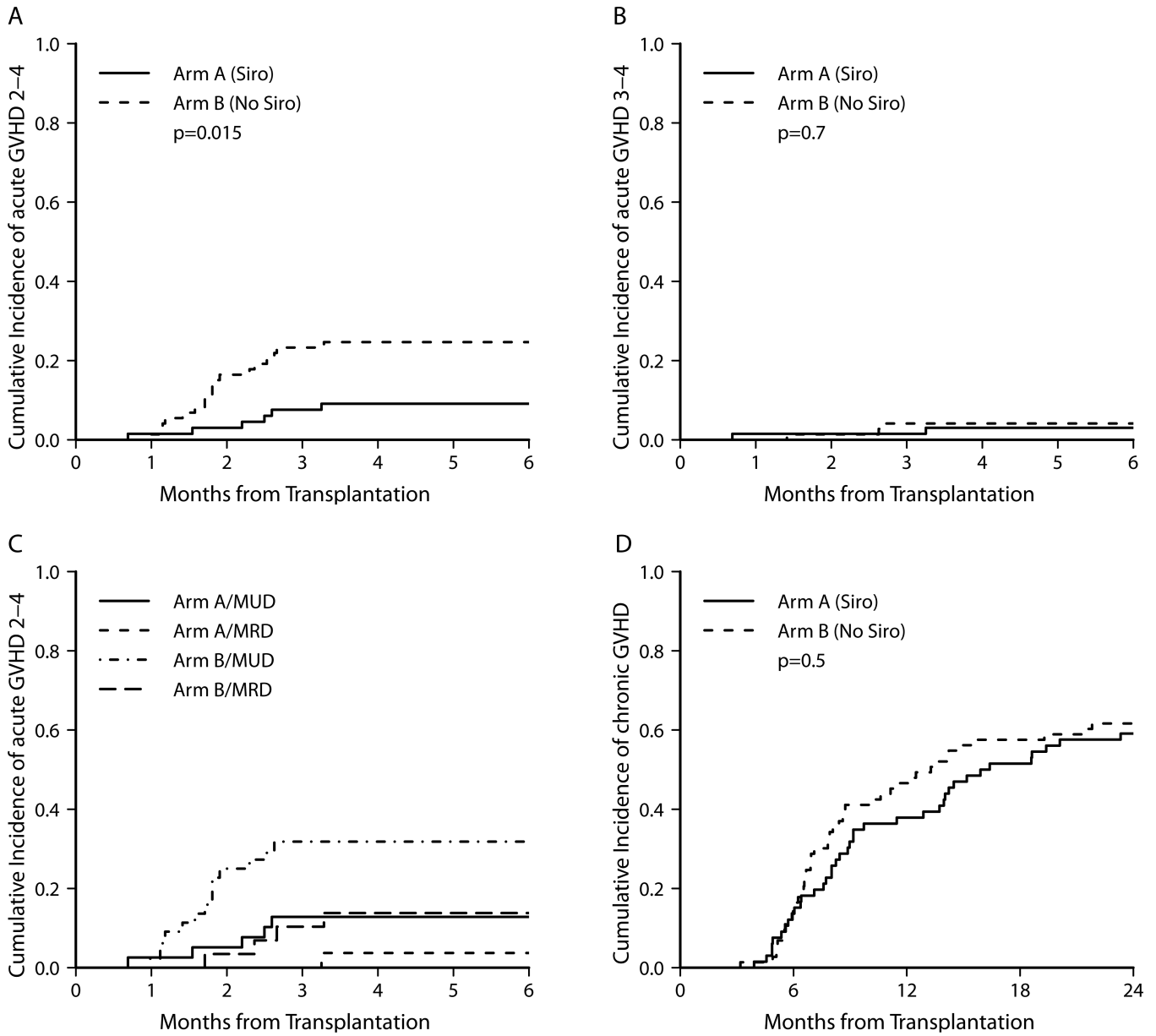
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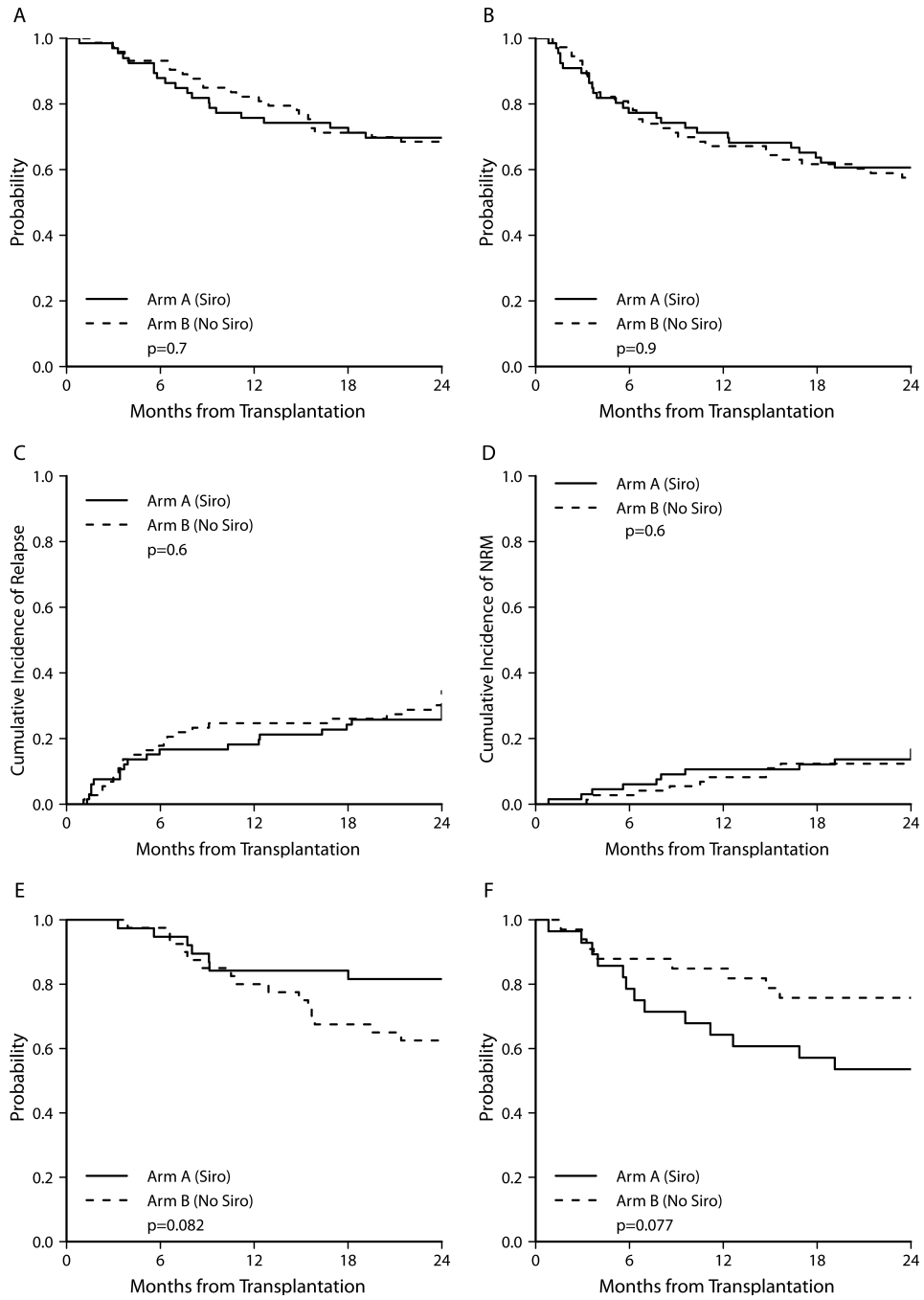
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**Figure 1. GVHD outcomes**

(A) Grade 2-4 acute GVHD, stratified by arm; (B) Grade 3-4 acute GVHD, stratified by arm; (C) Grade 2-4 acute GVHD, stratified by arm and donor type; (D) Chronic GVHD. GVHD, graft-versus-host disease; MUD, matched unrelated donor; MRD, matched related donor; Siro, sirolimus.



**Figure 2. Survival outcomes**

(A) Overall survival, stratified by arm; (B) Progression-free survival, stratified by arm; (C) Cumulative incidence of relapse/progression, stratified by arm; (D) Cumulative incidence of non-relapse mortality, stratified by arm; (E) Overall survival for patients with indolent B-cell non-Hodgkin lymphoma and Hodgkin lymphoma, stratified by arm; (F) Overall survival for patients with aggressive B-cell (including mantle cell) and T-cell non-Hodgkin lymphoma, stratified by arm. All analyses are on an intent-to-treat basis.

**Table I**

## Baseline patient characteristics

Variable	N (%) <sup>a</sup>			
	Arm A Tac/Sir/Mtx	Arm B Tac/Mtx or CSA/MMF	p value	Total
<b>N</b>	<b>66</b>	<b>73</b>		<b>139</b>
<b>Age, years; median, (range)</b>	58 (23-70)	57 (23-69)	0.4	57 (23-70)
<b>Histology</b>			1.0	
Indolent B-NHL	28 (42)	31 (42)		59 (42)
Aggressive B-NHL/MCL	20 (30)	23 (32)		43 (31)
T-NHL	8 (12)	10 (14)		18 (13)
Hodgkin lymphoma	10 (15)	9 (12)		19 (14)
<b>Prior autologous transplant</b>	34 (52)	31 (42)	0.3	65 (47)
<b>Status at HSCT<sup>b</sup></b>			0.2	
CR	34 (52)	32 (44)		66 (47)
PR	28 (42)	28 (38)		56 (40)
SD	2 (3)	9 (12)		11 (8)
PD	2 (3)	4 (5)		6 (4)
<b>Donor</b>			1.0	
MRD	27 (41)	29 (40)		56 (40)
MUD	39 (59)	44 (60)		83 (60)
<b>Conditioning</b>			0.8	
Bu/Flu	63 (95)	69 (95)		130 (95)
Flu/Cy/TBI	3 (5)	4 (5)		7 (5)
<b>GVHD prophylaxis</b>			N/A	
Tac/Sir/Mtx	66 (100)			66 (47)
Tac/Mtx		69 (95)		69 (50)
CSA/MMF		4 (5)		4 (3)

Tac/Sir/Mtx, Tacrolimus/Sirolimus/Methotrexate; CSA/MMF, ciclosporin/mycophenolate mofetil; NHL, non-Hodgkin lymphoma; MCL, mantle cell lymphoma; HSCT, haematopoietic stem cell transplantation.

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; MRD, matched related donor; MUD, matched unrelated donor; Bu/Flu, busulfan/fludarabine; Flu/Cy/TBI, fludarabine/cyclophosphamide/total body irradiation; GVHD, graft-versus-host disease; N/A, not applicable

<sup>a</sup> Percentages may not add to 100 because of rounding.

<sup>b</sup> Unknown for 2 patients.

**Table II**

Summary of toxicity.

Adverse event	Arm A (n=66 patients) Tac/Sir/Mtx	Arm B (n=73 patients) Tac/Mtx or CSA/MMF
Grade 3-4 Events <sup>a</sup>		
<b>TMA/renal failure/haemolysis</b>	<b>15</b>	<b>8</b>
<b>Neutropenia</b>	<b>12</b>	<b>16</b>
<b>Thrombocytopenia</b>	<b>13</b>	<b>14</b>
<b>Leucopenia</b>	<b>6</b>	<b>9</b>
<b>Infection</b>	<b>9</b>	<b>18</b>
<b>Hyperlipidaemia</b>	<b>2</b>	<b>2</b>
Anorexia	2	1
Cataract	2	1
Confusion/psychosis/encephalopathy	8	8
Diarrhoea	3	4
Haematoma	2	1
Hyperglycaemia	3	3
Respiratory	7	10
Hepatic	4	15
Stomatitis/mucositis	1	4
Nausea/vomiting	4	1
Abdominal pain	1	5
Neuropathy	4	0
Weakness	3	1
Thrombosis	2	10
Allergic reaction	0	2
Cardiac	3	8
Dehydration	1	2
Oedema	1	2
Pain	1	8
Hyponatraemia	1	2
Hypotension	1	2
Rash	1	4
<b>Total grade 3-4 events</b>	<b>128</b>	<b>194</b>

Events of interest given their possible association with sirolimus are bolded.

TMA, thrombotic microangiopathy

<sup>a</sup>Only events reported in >1 patient on at least one of the arms are listed.