with cGVHD may amplify subsequent BCR-signaling and contribute to the pathophysiology of cGVHD. Thus, small molecule inhibitors of Syk may represent a potential therapeutic option for patients with cGVHD.

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A Multi-Center, Randomized, Double Blind, Phase III Clinical Trial Comparing Steroids/Placebo Vs. Steroids/Mycophenolate Mofetil As Initial Therapy for Acute Graft-Versus-Host Disease. Blood and Marrow Transplant Clinical Trials Network Study 0802

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Steroids are accepted standard primary therapy for aGvHD, but durable responses are infrequent. A prior trial conducted by the BMT CTN (0302) tested the addition of 1 of 4 agents to steroids as initial therapy and found mycophenolate mofetil (MMF) to be the most promising for further investigation. In this context, a phase III, multi-center randomized trial BMT CTN 0802, sponsored by the NHLBI and NCI, was initiated to test the addition of MMF/placebo to steroids as initial therapy for aGvHD. Patients with any grade of newly diagnosed aGvHD were eligible if they required systemic therapy. The primary study objective was GvHD free survival at day 56 after initiation of therapy. All patients received prednisone at 2 mg/kg/day (or equivalent) with either MMF (1000mg PO/IV q8h or 20 mg/kg for patients <60kg) or placebo. Taper of steroids was allowed no sooner than 3 days into study therapy, at the discretion of the treating physician, but the protocol required treatment with prednisone at a dose of at least 0.25 mg/kg/day of prednisone until day 28. MMF was continued until day 56 or until steroid discontinuation if sooner. Patients who developed aGvHD while on MMF prophylaxis or after unplanned DLI were excluded. Patients who had previously received MMF for prophylaxis were eligible if they had not received any MMF in the previous week. All patients needed to be engrafted. The study specified a futility rule for GVHD free survival at day 56 and the rule was met at a planned interim analysis after 236 patients (out of 372) were enrolled from 36 centers: 117 to MMF, 119 to placebo. Baseline characteristics were well balanced between treatment groups. Grade of GvHD at randomization was I/II (65%), III (28%) and IV (6%). GvHD free survival at day 56 after randomization was: MMF 69 pts (60.5%; 95% CI 51.6-69.5), placebo 60 pts (52.2%; 95% CI 43.0-61.3) $P = .78$. Chronic GvHD developed in 38 patients on MMF: 6 month (mo) estimate: 23.7% (95% CI 15.9-31.6), and 39 patients on placebo: 6 mo estimate: 26.5% (95% CI 18.3-34.7) $P = .69$. Overall survival at 6 mo, EBV reactivation, cumulative incidence of severe, life threatening, or fatal infections were similar. Cytopenias were more common in the MMF arm, while hyperglycemia was more common in the placebo arm. Cumulative incidence estimates for non relapse mortality at 6 mo was similar in both arms: MMF 15.5% vs. placebo 20.1%. p=0.83. Estimated 6 mo overall survival was 71.3% for MMF and 73.8% for placebo $P = .25$. The addition of MMF to steroids as first line therapy for patients with aGvHD does not result in improved GvHD free survival compared to treatment with steroids alone.

	MMF (n=117)	Placebo (n=119)	*P* value
GvHD free survival at day 56	61% (52-70%)	52% (43-61%)	0.78 *
CGvHD at 6 mo	24% (16-32%)	27% (18-35%)	0.69 †
Non relapse mortality at 6 mo	16% (9-22%)	20% (13-28%)	0.83 †
Overall survival at 6 mo	71% (62-79%)	74% (65-81%)	0.25‡

* Chi-square test.
† Gray's test.
‡ Log-rank test.

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Prospective Evaluation of A 'Two-Pronged' Strategy of Atorvastatin Administration As Acute Graft-Versus-Host Disease (aGVHD) Prophylaxis, to Both Donors and Recipients of Matched Related Donor (MRD) Allogeneic Hematopoietic Cell Transplantation (alloHCT)

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Atorvastatin (ATOR) is a potent immunomodulatory agent that holds promise as a novel and safe agent for aGVHD prophylaxis. In murine models ATOR administration to both donor and recipient mice, prevented aGVHD by inhibiting donor T-cell proliferation, inducing TH-2 polarization, and by inhibiting recipient antigen presenting cell function.

We conducted a phase II study (NCT01175148) to evaluate the safety and efficacy of ATOR administration for aGVHD prophylaxis, to both adult donors and recipients of MRD alloHCT. As aGVHD prophylaxis, ATOR (40mg/day PO) was administered to sibling donors, starting 14-28 days before the anticipated 1st day of stem cell collection. In alloHCT recipients aGVHD prophylaxis consisted of tacrolimus, micro-dose methotrexate and ATOR (40mg/day) administered from day -14 to day +180. *Ex vivo* or *in vivo* T-cell depletion was not permitted. Primary outcomes were rate of grade (Gr) II-IV aGVHD at day 100 and safety of ATOR administration to alloHCT donors/recipients. We tested the null hypothesis H_0: $p \geq 35\%$, vs. the alternate H_1: $p \leq 15\%$; where p is the probability of Gr II-IV aGVHD at day 100.