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Blood 142 (2023) 777–779

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Topical Ruxolitinib for Chronic Cutaneous GvHD: Promising Results of a Phase 2 Clinical Trial

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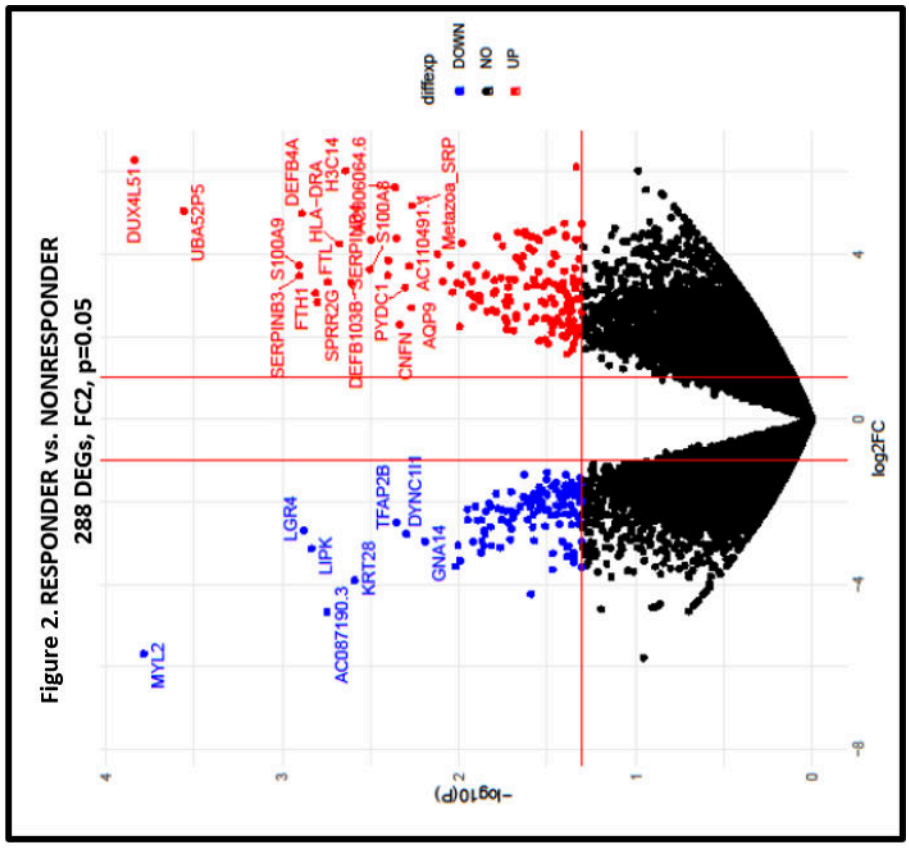
Background: Oral ruxolitinib is FDA-approved for the treatment of acute and chronic graft-versus-host disease (cGvHD), and ruxolitinib cream has been approved for the treatment of atopic dermatitis and vitiligo. Topical corticosteroids are the mainstay of skin-directed therapy for cutaneous cGvHD but are associated with significant side effects, and may incompletely treat cutaneous cGvHD thereby prompting the use of systemic therapies.
Methods: We conducted a single-center, phase 2 prospective, randomized, double-blind trial evaluating the efficacy and safety of ruxolitinib 1.5% cream in patients ≥12 years old with cutaneous nonsclerotic (lichen planus-like, poikilodermatous) and superficially sclerotic (lichen sclerosus, morphea-like) cGvHD with ≥2% of body surface area (BSA) affected. Patients were eligible if systemic therapy, when applicable, was stable for ≥4 weeks and concurrent topical therapy (including phototherapy) was not used. Patients were randomly assigned (1:1) to receive ruxolitinib 1.5% cream to the left or right side of face/body with placebo vehicle cream to contralateral side twice daily for 28 days. The primary endpoint was efficacy at Day 28, as measured by BSA of the GvHD rash on the side of face/body treated with ruxolitinib cream vs contralateral side treated with vehicle. Secondary endpoints included Physician's Global Assessment (PGA), and Composite Assessment of Index Lesion Severity (CAILS) at Days 14 and 28. For the exploratory endpoint, skin samples were noninvasively collected using the SmartSticker™ and RNA-sequencing was used to investigate gene expression differences between 1) ruxolitinib and vehicle treatments, and 2) responders (PGA 0-4) and nonresponders (PGA 5-6) at Day 28.
Results: Between 6/28/19 - 9/08/22, 24 patients (median age 47.5 years (range 18-78 years; 11 [46%] male) underwent randomization; Day 14 and Day 28 assessments were completed by 22 and 23 patients, respectively. Most patients had a history of acute leukemia (N=16 [67%]) or non-Hodgkin lymphoma (N=4 [16%]). Median time from transplant to enrollment was 455 days (IQR 357-1020), and from cGvHD onset to enrollment 132 days (IQR 19-384). Most patients had cutaneous nonsclerotic cGvHD (N=21, 87%) with lichen planus-like (N=11), papulosquamous (N=7), and maculopapular rash/erythema features (N=3). Three patients had lichen sclerosus-like cGvHD. Patients were heavily pretreated and had a median of 2 prior systemic treatments. Most patients had failed ≥2 topical therapies: 88% failed topical steroids, 42% topical calcineurin inhibitors, and 29% phototherapy. BSA of cGvHD on the treatment side compared to the vehicle side was significantly improved from Day 1 (14.4 vs 14.5% on treatment/vehicle; p=0.12) to Day 14 (7.7 vs 10.4; p=0.002) to Day 28 (6.2 vs 10.4; p=0.003), respectively. Both secondary endpoints were significantly improved with treatment starting on Day 14 and continuing into Day 28 (PGA D1: 5 treatment vs 5 vehicle; D14: 2.7 vs 3.8, p=0.002; D28: 1.9 vs 3.7, p=0.0004. CAILS D1: 15 treatment vs 15.3 vehicle, p=0.12; D14: 6.9 vs 11, p=0.0009; D28: 5.8 vs 10.6, p=0.004). Seven patients experienced 16 treatment-emergent AEs, the most commonly observed was orofacial dermatitis attributed to protective mask use (n=2). One grade 1 headache was possibly attributed to therapy. RNA sequencing from 22 ruxolitinib- and vehicle- treated patient pairs at Day 28 identified 324 differentially expressed genes (DEGs, fold change (FC)> 2; adjp=0.05) with primary pathway differences in translocation of ZAP-70 to immunological synapse, PD-1 signaling, and Th17 cell differentiation (**Figure 1**). Additionally, 288 DEGs (FC>2;

p=0.05) were identified between responders (n = 17) and nonresponders (n = 5) at Day 28 (**Figure 2**) with pathway differences in IL-12 signaling. Responders had upregulated expression of LCP1 and SOD2, while nonresponders had upregulation in CA1 and SNRPA1.

Conclusions: This is the first study to characterize the effect of topical JAK1/2 blockade on cutaneous cGVHD. Ruxolitinib 1.5% cream was safe and effective compared to placebo in treating cutaneous nonsclerotic and superficially sclerotic GvHD. Responders to ruxolitinib cream had genomic signature differences in IL-12 signaling from nonresponders. These encouraging results support a larger clinical trial to further evaluate the efficacy and safety of topical ruxolitinib in patients with cutaneous cGvHD.

Disclosures Markova: *Protagonist Therapeutics, Inc.:* Consultancy, Research Funding; *Incyte Corporation:* Research Funding; *Amryt Pharma:* Research Funding; *ADC Therapeutics:* Consultancy; *AstraZeneca:* Consultancy; *Blueprint Medicines:* Consultancy; *Alira Health:* Consultancy; *OnQuality:* Consultancy; *Janssen:* Consultancy; *UpToDate:* Patents & Royalties: Royalties. **Ostojić:** *DermTech:* Current Employment. **Ai:** *DermTech:* Current Employment. **Lacouture:** *Apricity:* Consultancy; *Roche:* Consultancy; *OnQuality:* Consultancy; *Lutris:* Consultancy; *Seattle Genetics:* Consultancy; *Loxo:* Consultancy; *Genentech:* Consultancy; *Trifecta:* Consultancy; *RBC/La Roche Posay:* Consultancy; *Kintara:* Consultancy; *Deciphera:* Consultancy; *Novartis:* Consultancy; *Janssen:* Consultancy; *Novocure:* Consultancy; *Johnson and Johnson:* Consultancy, Research Funding; *AstraZeneca:* Research Funding; *Oncoderm:* Consultancy. **Gyurkocza:** *Actinium Pharmaceuticals, Inc:* Research Funding. **Shaffer:** *Hansa Biopharma:* Consultancy; *Gamida Cell:* Consultancy, Research Funding. **Scordo:** *Omeros Corporation:* Consultancy, Research Funding; *Angiocrine Bioscience, Inc.:* Research Funding; *Amgen, Inc.:* Research Funding; *Medscape, LLC:* Honoraria; *Cancert-Network (Intellisphere LLC):* Honoraria. **Perales:** *BMS:* Consultancy, Honoraria; *Astellas:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Incyte:* Consultancy, Honoraria, Research Funding; *Allogene:* Research Funding; *MorphoSys:* Consultancy, Honoraria; *VectivBio AG:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *NexImmune:* Consultancy, Current equity holder in publicly-traded company; *Novartis:* Consultancy, Honoraria, Research Funding; *Nektar Therapeutics:* Consultancy, Honoraria, Research Funding; *Caribou:* Consultancy, Honoraria; *Allovir:* Consultancy; *Miltenyi Biotec:* Consultancy, Honoraria, Research Funding; *DSMB:* Other; *Servier:* Other; *Medigene:* Consultancy, Other; *Syncopation:* Honoraria; *Equillium:* Consultancy, Honoraria; *Omeros:* Consultancy, Current equity holder in publicly-traded company, Honoraria; *Cidara Therapeutics:* Consultancy, Other; *Sellas Life Sciences:* Consultancy; *Vor Biopharma:* Consultancy, Honoraria; *Kite:* Consultancy, Honoraria, Research Funding; *Miltenyi Biotec:* Honoraria; *Exevir:* Consultancy, Honoraria; *Orcabio:* Consultancy, Current equity holder in publicly-traded company, Honoraria; *Merck:* Consultancy, Honoraria; *Karyopharm:* Consultancy, Honoraria; *Celgene:* Honoraria; *Adicet:* Honoraria. **Harris:** *Horizon Pharma PLC:* Consultancy; *Incyte Corporation:* Consultancy, Research Funding; *Janssen Scientific Affairs, LLC:* Consultancy. **Ponce:** *Kadmon/Sanofi Pharmaceuticals:* Membership on an entity's Board of Directors or advisory committees; *Ceramedix:* Membership on an entity's Board of Directors or advisory committees; *Incyte Corporation:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Evive Biotechnology:* Membership on an entity's Board of Directors or advisory committees.

https://doi.org/10.1182/blood-2023-182198



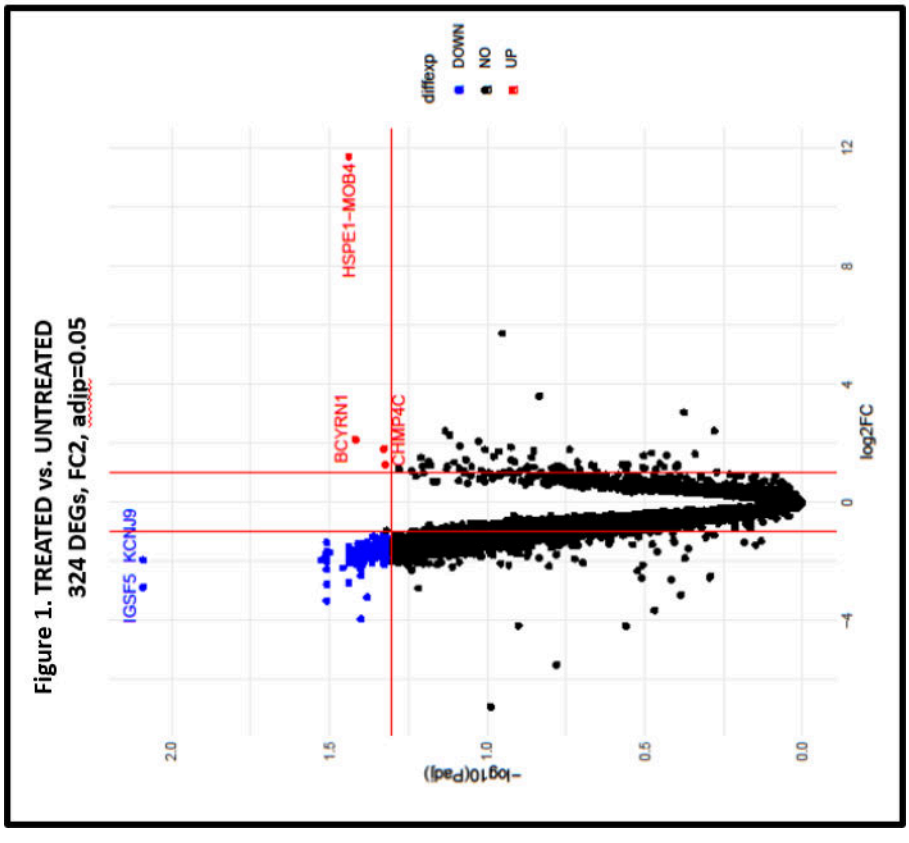


Figure 1