ELSEVIER

Blood 142 (2023) 184–186

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

624.HODGKIN LYMPHOMAS AND T/NK CELL LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Post-Allograft Romidepsin Maintenance Mitigates Relapse Risk and Stimulates the Graft-Versus-Malignancy Effect through Enhanced NK-Cell Cytotoxicity in Patients with T-Cell Malignancies: Final Results of a Phase I/II Trial

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Background: For patients with high risk, and relapsed/refractory T-cell malignancies allogeneic stem cell transplant (allo-SCT) is the only available potentially curative therapy. The efficacy of allo-SCT is limited in this population by high rates of relapse, with rates up to 55-60% post-allo-SCT. We designed a phase I/II trial, evaluating the combination of the histone deacetylases inhibitor romidepsin (rom) with busulfan/fludarabine (BuFlu) conditioning, followed by romidepsin maintenance (m-rom) in patients receiving allo-SCT for T-cell malignancies (NCT02512497). Here we present final clinical results of this therapeutic approach, including an evaluation of the stimulatory effects of m-rom on the graft-versus-malignancy effect through NK-cells post-allo-SCT.

Methods:
This was a phase I/II clinical trial. Eligible patients had: a diagnosis of T-cell leukemia (including T-acute lymphoblastic leukemia) or T-cell lymphoma (TCL, cutaneous or peripheral) in at least a partial remission requiring an allo-SCT, <70 years of age, with a matched sibling/unrelated donor. Patients received myeloablative (20K) or reduced intensity (16K) BuFlu with rom, followed by standard tacrolimus/methotrexate GVHD prophylaxis and anti-thymocyte globulin for unrelated donors (MUD). An expansion cohort of up to 30 patients (total) was included. M-rom was initiated between day +28 and +100 for 1 year (2 nd year optional), with built in dose reductions for toxicity. An efficacy endpoint of 20% reduction in relapse risk at 1-year in the whole cohort or any individual disease cohort was set based upon historical/CIBMTR (Center for Blood and Marrow Transplant Research) controls was pre-specified. The effect of m-rom on NK-cell cytotoxicity was assessed on samples taken pre-transplant, and

1, 3, 6, 12 months post allo-SCT. NK cytotoxicity was assessed by isolating mononuclear cells from patient samples at each timepoint, comparing those on m-rom (n=13) versus those who did BuFlu controls who did not receive m-rom (n=16). Cells were targeted against K562 targets using the calcein-AM assay. K-M and Fine-Gray models were used to estimate PFS, OS, and cumulative incidence, and compare survival across groups.

Results:

28 patients were enrolled on this trial (Table). With a median follow-up time of 15 months, the median OS is 3.3 years (95% CI: 0.85-not reached), with a 1 and 3 year OS probability of 68% and 54%. The median PFS is 2.3 years (95% CI: 0.6-not reached), with 1 and 3-year PFS of 61% and 41%. Cumulative incidence (CI) of NRM at day 100 and 1 year were 14.3% and 21.4%. CI of grade II-IV aGHVD and extensive cGVHD were 46.4% and 38%. The CI of relapse (CIR) was 18.1% at 1 year and 33% at 3 -years. There was no difference between PFS among patients with MRD versus those without MRD prior to transplant (p=0.43).

The CIR of patients with TCL was 9.3% at 1 and 3 years, whereas the CIR of patients with leukemia was 25% at 1 year and 48% at 3 years. No patients with PTCL relapsed, 1/2 patients with CTCL relapsed, and 4/6 patients with T-PLL are alive, disease free. Pre-specified general CIR was 55% for all patients. With an overall CIR of 18% at 1 year, and 33% at 3-years, this trial met its pre-specified endpoint of decreasing relapse by 20% at 1-year, and performed well compared to published CIBMTR control populations. Matched propensity score analysis across disease subsets with CIBMTR controls will be presented.

18/28 (64%) of patients received m-rom with a median number of 13 cycles (range 1-47). 8 patients experienced grade 3/4 adverse events (AE), and 1 patient discontinued m-rom due to toxicity, unlikely related to romidepsin (loss of CD3 chimerism). When NK-cytotoxicity was assessed between the two groups after starting maintenance, NK-cytotoxicity in the m-rom group was significantly higher than in those without m-rom ($p<0.0001$) (Figure).

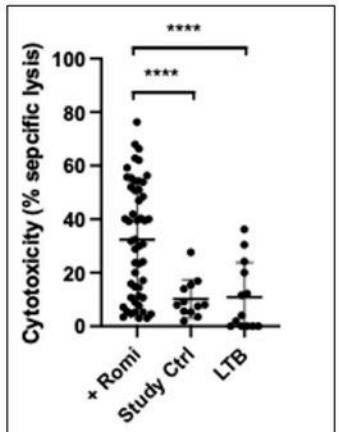
Conclusions:

BuFluRom with m-rom is effective at decreasing relapse in patients with T-cell malignancies, with 1-year CI relapse below expected relapse rates for this set of diseases, meeting the pre-specified efficacy endpoint. NK-cell cytotoxicity data in a large sample set of trial patients demonstrates that m-rom enhances NK-cell cytotoxicity post allo-SCT, augmenting the GVL effect and likely accounting for at a minimum, some of the decrease in relapse seen on this trial. M-rom should be considered a new option post allo-SCT to mitigate relapse in patients with T-cell malignancies.

Disclosures Vasu: *Omeros Inc:* Research Funding; *Sanofi Inc:* Research Funding. **Wall:** *Abbvie, BMS:* Honoraria; *CTI:* Speakers Bureau. **Jaglowski:** *Kite. a Gilead Company:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *Bristol-Myers Squibb:* Consultancy, Research Funding; *Takeda:* Consultancy; *CRISPR:* Consultancy; *Caribou:* Research Funding. **Choe:** *NIH National Cancer Institute:* Research Funding; *Actinium Pharmaceuticals:* Other: Support for attending meetings and/or travel; *MJH Life Sciences:* Honoraria; *Opna:* Other: Receipt of equipment, materials, drugs to institution, Research Funding; *Incyte:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Receipt of equipment, materials, drugs to institution. **Champlin:** *Takeda Corporation:* Patents & Royalties; *Cell Source:* Research Funding; *Johnson & Johnson/Janssen:* Consultancy; *Orca Bio:* Consultancy; *Omeros:* Consultancy; *Arog:* Consultancy; *Kadmon:* Consultancy; *Actinium Pharmaceuticals:* Consultancy. **de Lima:** *Pfizer:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Scribb:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Other: Data Safety Monitoring Board; *AbbVie:* Other: Data Safety Monitoring Board; *Miltenyi Biotec:* Research Funding. **Lee:** *Kiadis Pharma, a Sanofi Corporation:* Consultancy, Patents & Royalties: licensed through Nationwide Children's Hospital; *Avidicure B.V.:* Consultancy, Current equity holder in private company, Research Funding. **Brammer:** *Verastem:* Research Funding; *Seattle Genetics:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Kymera:* Consultancy; *Incyte:* Research Funding; *Dren Bio:* Consultancy; *Bristol Myers Squibb:* Research Funding.

OffLabel Disclosure: This off label use is part of a clinical trial.

Subject	Age/Sex	Disease	Disease Status	Donor	Status	Maintenance	Reason for DC Or Not starting
MDACC1	54 M	MF/ALCL	CR	MRD	CR	8 cycles	Preference
MDACC2	35 M	ETP-ALL	CR1	MRD	Died/Relapse	1 cycle	Cytopenias
MDACC3	43 M	ETP-ALL	CR1	MUD	CR	23 cycles	EOT
MDACC4	48 F	SPLTCL (Stage IV)	PR	MRD	CR	1 cycle	Pt Declined
MDACC5	58 M	T-PLL	CR	MUD	CR	0 cycles	Declined
MDACC6	60 F	T-PLL	PR	MRD	Died/aGVHD	Died (aGVHD)	Pt Deceased
OSU-7	59 F	PTCL	CR	MUD	CR	0 cycles	GVHD
OSU-8	48 M	AITL	PR	MUD	Died (NRM)	0 cycles	AKI
OSU-9	38 F	ATLL	CR1	MUD	Deceased	10 cycles	Relapse
OSU-10	67 F	T-PLL	CR1	MUD	CR	16 cycles	EOT
OSU-11	51 F	T-ALL	CR1	MUD	Died (NRM)	0 cycles	Deceased
OSU-12	63 F	T-PLL	CR1	MUD	Died/Relapse	0 cycles	Relapse
OSU-13	45 M	T-PLL	CR1	MUD	CR	12 cycles	Compliance
OSU-14	45 M	ETP-ALL	PR	MUD	Alive	43 cycles	EOT
OSU-15	58 M	T-ALL	CR2	MRD	Died/Relapse	8 cycles	Relapse
OSU-16	21 F	SPLTCL	CR2+	MUD	CR	16 cycles	cGVHD
OSU-17	58 F	T-ALL	CR1	MRD	Died (NRM)	None	Deceased
OSU-18	27 M	ETP-ALL	CR1	MUD	CR	39 cycles	N/A
OSU-19	65 F	PTCL	CR1	MUD	CR	29 cycles	DCIS Dx
OSU-20	51 M	CTCL	CR2+	MUD	Died/Relapse	11 cycles	Low CD3
OSU-21	56 M	HSTCL	CR1	MUD	Died (NRM)	3	Infection
OSU-22	58 F	PTCL	CR2	MUD	CR	13 Cycles	DCIS Dx
OSU-23	66 F	T-ALL	CR2+	MUD	Died/ (NRM)	None	Deceased
OSU-24	56 M	PTCL	CR1	MUD	CR	None	Deceased
OSU-25	65 F	ALCL	PR	MUD	CR	None	Low CD3
OSU-26	66 M	T-PLL	CR1	MUD	CR	27 cycle	On treatment
OSU-27	26 F	AITL	CR2	MUD	CR	3	GVHD
OSU-28	57 M	T-ALL	CR1	MUD	CR	15 cycles	EOT



NK-cytotoxiciy was enhanced with m-rom post-allo-SCT when compared to study controls without m-rom and banked allo-SCT recipients (LTB).
**** p<0.0001

Figure 1

https://doi.org/10.1182/blood-2023-190213