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622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

Potent CD8+ T-Cell Proliferation and Effector Differentiation Following Subcutaneous (SC) Mosunetuzumab Administration in Patients with Untreated, High Tumor-Burden Follicular Lymphoma (FL)

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Introduction:
Bispecific antibodies (BsAb) have emerged as a potent therapeutic option for patients with B-cell non-Hodgkin lymphoma, including FL. These drugs leverage endogenous CD3+ T-cells to enable cytotoxic tumor cell killing. While their mode of action has been hypothesized in *in vitro* and animal models, the mechanisms by which these drugs promote both initial and long-term immune-dependent disease control remains unknown. We recently initiated a multicenter phase 2 trial of the CD20xCD3 BsAb mosunetuzumab (mosun) as first-line therapy for patients with high-burden FL (NCT05389293). As part of this study, we performed serial sampling of both blood and lymph node tissues in order to elucidate T-cell changes associated with response and outcome. Here we present the first analysis of peripheral blood immune profiling.

Methods:
Patients with untreated, high-burden stage 2-4 FL in need of treatment received SC mosun at the dose of 5 mg on D1 and 45 mg on D8 and D15 of C1, and 45 mg on D1 of each subsequent 21-day cycle. Peripheral blood samples were obtained on C1D1, C1D8, C1D15, C2D1, C3D1, C5D1, and end of treatment (EOT, 24w from C1D1). Peripheral blood mononuclear cells (PBMCs) and plasma were isolated and cryopreserved. Samples were later thawed in batches and processed as follows: CITE-Seq + single-cell TCR sequencing was performed on viable CD11b-/CD19-/CD56-/CD3+ T-cells using the 10x Genomics Single Cell Immune Profiling Platform. RNA was extracted from 1 x 10^6 viable PBMCs using TriZol, followed by phenol/chloroform-based extraction, followed by bulk TCR sequencing using an in-house platform developed by MSKCC's Integrated Genomics Operation. The remaining cells were stained with antibodies targeting CD45RA, CD8, CD45, CD45RO, CD38, CD27, CD28, CXCR3, LAG-3, CD3, CD4, HLA-DR, CXCR5, CCR6, CD56, CD11b, CD19, CD39, PD-1, OX40, Tim-3, CCR4, Granzyme B, T-bet, FoxP3, Ki-67, and CTLA-4 and analyzed using a Cytek Aurora Spectral Cytometer. Flow cytometry analysis was performed using OMIQ. Statistical analyses were performed using a paired t-test.

Results:
A total of 45 samples obtained from 8 patients were analyzed, including samples from C1D1 (8), C1D8 (6), C1D15 (3), C2D1 (7), C3D1 (8), C5D1 (6), and EOT (7). High dimensional clustering of spectral cytometry data using the FlowSOM algorithm revealed 9 clusters of CD8+ T-cells corresponding to known CD8+ T-cell subsets. Among these subsets, we observed two distinct temporal patterns of CD8+ T-cells within the blood. On C1D8 there was a profound drop in circulating effector CD8+ T-cells as well as terminally differentiated CD8+ Temra cells (Figure 1), with a corresponding enrichment of naïve CD8+ T-cells (Figure). We also observed significant proliferation of newly activated T-cells on C1D8, followed by expansion of CD8+ T-cells expressing several activation and exhaustion markers including PD-1, Tim-3, and CD39, peaking on C2D1 (Figure 2). CD4+ T-cell responses were more modest with a small early increase in CD28+OX40+PD-1+ CD4+ T-cells on C1D8 and a drop in circulating GzmB+OX40+ CD4+ T-cells on C1D15.

Conclusion:

SC mosun therapy for newly diagnosed FL was associated with a unique peripheral blood immune profile, with early mobilization of pre-differentiated CD8+ T-cell effector cells and subsequent activation and expansion of newly primed CD8+ T-cells. Further immune phenotyping, including scRNA-seq and TCR clonal dynamics in the peripheral blood over time, as well as TCR clonality of distinct CD8+ and CD4+ T-cell populations are currently being analyzed on these and additional samples, and will be presented in detail.

Disclosures Falchi: *Abbvie:* Consultancy, Other: Advisory Board, Research Funding; *Genentech:* Consultancy, Other: Advisory Board, Research Funding; *Seagen:* Other: Advisory Board; *ADC Therapeutics:* Other: Advisory Board; *AstraZeneca:* Consultancy; *Roche:* Consultancy, Research Funding; *Genmab:* Consultancy, Research Funding. **Ghione:** *Kite, A Gilead Company:* Research Funding; *Secura Bio:* Consultancy; *AstraZeneca Pharmaceuticals:* Consultancy; *Kyowa Hakko Kirin:* Consultancy. **Hamlin:** *ADC Therapeutics:* Consultancy. **Lue:** *Merck:* Consultancy; *OncLive:* Consultancy. **Epstein-Peterson:** *Kymera:* Research Funding; *Viracta:* Research Funding; *Amgen:* Research Funding; *OncLive:* Honoraria; *WebMD:* Honoraria. **Kumar:** *Adaptive Biotechnologies:* Research Funding; *Celgene:* Research Funding; *Astra Zeneca:* Consultancy, Research Funding; *Genentech:* Consultancy, Research Funding; *Pharmacyclics:* Research Funding; *Loxo/Lily Oncology:* Consultancy, Research Funding; *BridgeBio:* Current equity holder in publicly-traded company; *Abbvie Pharmaceuticals:* Research Funding; *Janssen:* Consultancy; *Beigene:* Research Funding; *Seattle Genetics:* Research Funding; *Kite Pharma:* Consultancy. **Palomba:** *Juno:* Honoraria, Patents & Royalties; *Kite:* Honoraria; *Ceramedix:* Honoraria; *MustangBio:* Honoraria; *GarudaTherapeutics:* Honoraria; *Novartis:* Honoraria; *Pluto Immunotherapeutics:* Honoraria; *Rheos:* Honoraria; *Seres Therapeutics:* Honoraria, Patents & Royalties; *Smart Immune:* Honoraria; *Thymofox:* Honoraria; *Synthekine:* Honoraria; *Cellectar:* Honoraria; *BMS:* Honoraria. **Torka:** *Genentech:* Consultancy; *Genmab:* Consultancy; *ADC Therapeutics:* Consultancy; *TG Therapeutics:* Consultancy; *Lilly USA:* Consultancy; *Seagen:* Consultancy. **Zelenetz:** *None other than mutual funds (401K):* Current equity holder in publicly-traded company; *BMS:* Consultancy, Honoraria; *SAB:* Membership on an entity's Board of Directors or advisory committees; *Lymphoma Research Foundation:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Consultancy, Honoraria; *Janssen Pharmaceuticals:* Consultancy, Honoraria; *F. Hoffmann-La Roche Ltd:* Consultancy, Honoraria, Research Funding; *Gilead:* Consultancy, Honoraria; *Pharmacyclics:* Consultancy, Honoraria; *Abbvie:* Research Funding; *BeiGene:* Consultancy, Honoraria, Research Funding; *MEI Pharma Inc:* Consultancy, Honoraria, Research Funding. **Salles:** *Genentech, Inc./F. Hoffmann-La Roche Ltd:* Consultancy, Research Funding; *Debiopharm:* Consultancy; *Molecular Partners:* Consultancy; *Loxo/Lilly:* Consultancy; *Merck:* Consultancy, Honoraria; *Genmab:* Consultancy; *ATB Therapeutics:* Consultancy; *BeiGene:* Consultancy; *AbbVie:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy; *Novartis:* Consultancy; *EPIZYME:* Consultancy; *Orna:* Consultancy; *Nurix:* Consultancy; *Ipsen:* Consultancy, Research Funding; *Nordic Nanovector:* Consultancy; *Owkin:* Current holder of *stock options* in a privately-held company; *Kite/Gilead:* Consultancy; *Janssen:* Consultancy, Research Funding; *Incyte:* Consultancy. **Vardhana:** *Koch Disruptive Technologies:* Consultancy; *Immunai:* Consultancy.

OffLabel Disclosure: Mosunetuzumab is FDA approved for the treatment of FL after 2+ lines of systemic therapy. Front-line SC mosunetuxumab is experimental

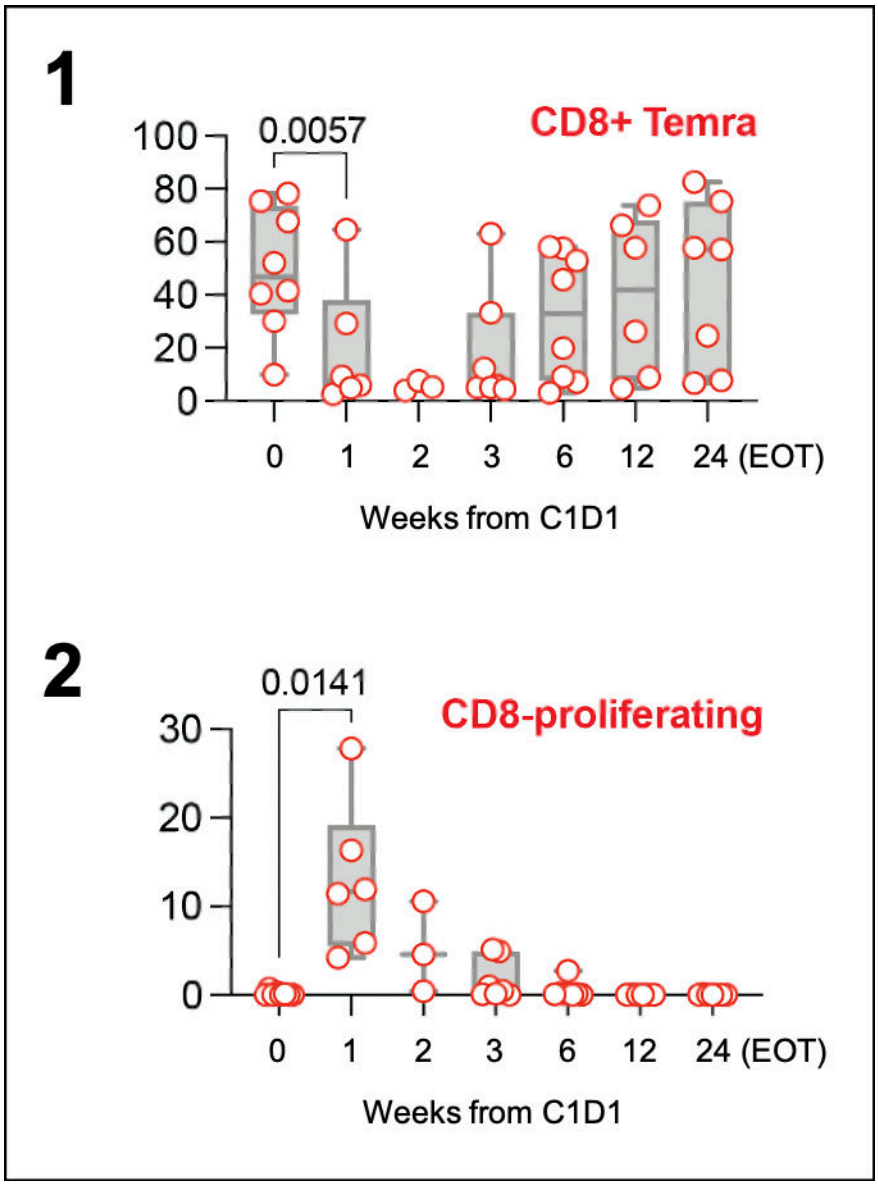

Figure 1

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