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POSTER ABSTRACTS

705.CELLULAR IMMUNOTHERAPIES: LATE PHASE AND COMMERCIALLY AVAILABLE THERAPIES

Poor Hematopoietic Reserve at the Time of CD19 CAR T-Cell Infusion Is Associated with Long Term B-Cell Aplasia

Grace Johnson[1], *Kedar Patel*[1], *Brian Arciola*[1], *Ariel Perez Perez, MD*[2], *Anthony Wood, MD*[3], *Filip Ionescu, MD*[3], *Jennifer M Logue, MD*[3,4], *Omar Albanyan, MD*[3], *Hassaan Yasin, MD*[3], *Christina A Bachmeier, PharmD*[3], *Kayla Reid, MS*[3], *Meghan Menges*[3], *Salvatore Corallo*[3], *Bijal D. Shah, MD*[3,1], *Julio C Chavez, MD*[5,1], *Farhad Khimani, MBBS*[3,1], *Taiga Nishihori, MD*[3,1], *Rawan Faramand, MD*[3,1], *Hien Liu, MD*[3,1], *Aleksandr Lazaryan, MD MPH, PhD*[3,1], *Kai Rejeski, MD*[6], *Marion Subklewe, MD*[7], *Fabiana Perna, MDPhD*[3,1], *Marco Davila, MD PhD*[8], *Rahul Mhaskar, MPH, PhD*[1], *Frederick L. Locke, MD*[3,1], *Michael D. Jain, MD PhD*[3,1]

[1] University of South Florida Morsani College of Medicine, Tampa, FL
[2] Miami Cancer Institute, Miami, FL
[3] Moffitt Cancer Center, Tampa, FL
[4] Moffitt Cancer Center at Memorial Health System, Pembroke Pines, FL
[5] Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL
[6] LMU University Hospital, Munich, Germany
[7] Department of Medicine III, LMU University Hospital, LMU Munich, Muenchen, Germany
[8] Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: On-target off-tumor toxicities of anti-CD19 CAR T-cell therapy include B-cell aplasia and hypogammaglobulinemia. Long term B-cell aplasia is hypothesized to represent functional CAR T-cell engraftment (Melenhorst, Nature 2022), while peripheral blood B-cell recovery represents the loss of functional CAR-T cells against target over time. Patients with large B-cell lymphoma (LBCL) who are clinical responders have a 50-70% chance of B-cell recovery in the first year, with the remainder experiencing longer term B-cell aplasia (Logue, Haematologica 2021). Here, we sought to identify factors associated with long term B-cell aplasia using a cohort of responding patients who received CAR T-cell therapy for LBCL.
*Methods:*This retrospective cohort study included 57 patients with LBCL treated with CD19-targeted CAR T-cell therapy between June 2016 and August 2020 at Moffitt Cancer Center who exhibited complete or partial response at six months after CAR T-cell infusion. Patients were treated with with axicabtagene ciloleucel (axi-cel; n=50) or tisagenlecleucel (tisa-cel; n=7), either as standard-of-care therapy (n=47) or as part of a previously published clinical trial (n=10; NCT02348216, NCT03391466, NCT03153462). Peripheral blood B-cells were measured by flow cytometry using CD19 expression as part of routine clinical care at baseline and periodically after infusion. Prolonged B-cell aplasia was defined as a CD19+ B cell count comprising less than 1% of peripheral blood mononuclear cells during a minimum of two separate time points beyond 6 months of follow-up. Patients were defined as having B cell recovery if >1% B-cells were observed in peripheral blood at any time after CAR T-cell infusion.
Results: At a median follow up of 33 months (95% CI: 28.7, 37.3 months), 29 (51%) patients had persistent B-cell aplasia and 28 (49%) had recovery of peripheral B-cell counts. Median B-cell count at 12 months in the recovery group was 84/μL (IQR 2.5-197) compared to 0/μL (IQR 0-1) in the aplasia group. Patients with long-term B-cell aplasia had lower CD4 T-cell counts prior to CAR T-cell infusion [median 200/μL (IQR 136-278) vs. 330/μL (IQR 224-451); P= 0.008] and over time compared to patients with B-cell recovery (Fig. A). Patients with long-term B cell aplasia also had lower pre-infusion absolute neutrophil counts (2.3K/μL (IQR 1.4-4.15) vs. 3.5K/μL (IQR 2.8-4.2); P<0.001) and higher baseline CAR-HEMATOTOX scores [2 (IQR 1-3.25) vs 1 (IQR 0-1)], consistent with poor baseline hematopoietic reserve (Rejeski, Blood 2021). While disease-related mortality did not significantly differ between groups, non-relapse mortality was markedly higher in patients with long-term B-cell aplasia due to infection: all 8 patient deaths in the aplasia group were due to infections occurring beyond day 30 post-infusion, with 6 of the 8 deaths due to COVID-19. However, no patients in the B-cell recovery group died of late infection (Fig. B).
Conclusions: Long term B-cell aplasia is hypothesized to represent ongoing CAR T-cell activity against normal B-cells. However, our results demonstrate that B-cell aplasia is associated with low baseline hematopoietic reserve and subsequent poor immune reconstitution of multiple lineages including B-cells, T-cells, and myeloid cells. Further studies are warranted to as-

sess whether poor immune reconstitution and B-cell aplasia are related to long term CAR T-cell activity or other processes. These patients are at higher risk for non-relapse mortality from infection, and mitigation strategies are needed.

Disclosures Perez Perez: *Gilead Kite:* Speakers Bureau. **Bachmeier:** *Kite Pharma:* Consultancy. **Shah:** *Incyte, Jazz Pharmaceuticals, Kite/Gilead, SERVIER:* Research Funding; *Celgene, Novartis, Pfizer, Janssen, Seattle Genetics, AstraZeneca, Stemline Therapeutics, Kite/Gilead:* Other: Travel, Accommodations, Expenses; *Pharmacyclics/Janssen, Spectrum/Acrotech, BeiGene, Gilead Sciences:* Honoraria; *DSMC, Pepromene Bio:* Membership on an entity's Board of Directors or advisory committees; *Moffitt Cancer Center:* Current Employment; *Takeda, AstraZeneca, Adaptive Biotechnologies, BMS/Celgene, Novartis, Pfizer, Amgen, Precision Biosciences, Kite/Gilead, Jazz Pharmaceuticals, Century Therapeutics, Deciphera, Autolus Therapeutics, Lilly, Pepromene:* Consultancy. **Chavez:** *Epizyme:* Speakers Bureau; *Cellectar:* Membership on an entity's Board of Directors or advisory committees; *BMS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Beigene:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; 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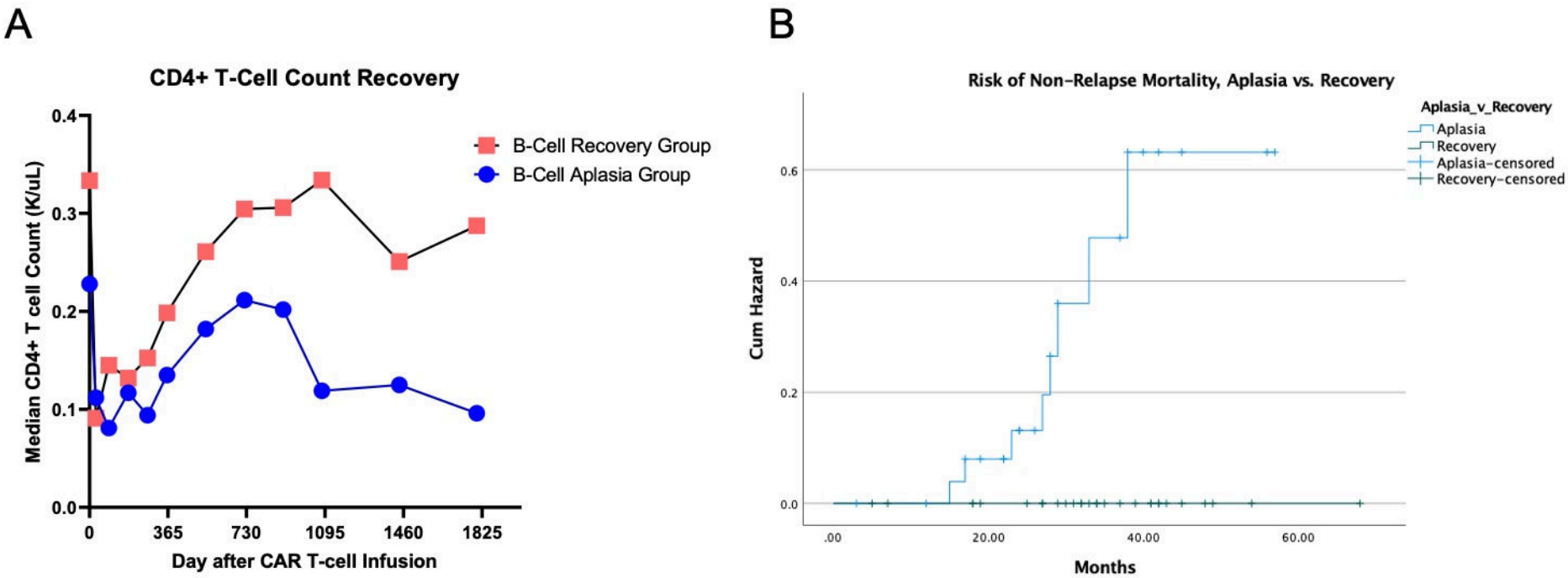

A) Median peripheral blood CD4 T-cell counts after CAR T-cell therapy. B) Six-month landmarked cumulative risk of non-relapse mortality. Log-rank P-value <0.001.

Figure 1