ELSEVIER

Blood 142 (2023) 4684–4685

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

BCMAxCD3 Bispecific Antibody Elranatamab Is Effective in Patient Myeloma Relapsed after BCMA CAR-T

Alana L. Keller, BS[1], *Sarah E. Parzych, BA*[1], *Lauren T. Reiman, BS*[1], *Zachary J. Walker, BS, MS*[1], *Peter A. Forsberg, MD*[2], *Daniel W. Sherbenou, MDPhD*[1]

[1] Division of Hematology, University of Colorado Anschutz Medical Campus, Aurora, CO
[2] Division of Hematology, University of Colorado Health Blood Disorders and Cell Therapies Center, Aurora, CO

Introduction: In recent years, therapies targeting the plasma cell-specific protein BCMA have been widely adopted into the treatment of patients with relapsed refractory multiple myeloma (MM). Agents include chimeric antigen receptor t cell therapies (CAR-Ts) and bispecific T cell engaging antibodies (bsAbs). Targeting BCMA is effective in late-stage, heavily pretreated patients, and studies are examining if these therapies work even better earlier in disease progression. As the number of available BCMA agents has rapidly expanded, guidance is lacking on how to sequence these therapies to maximize patient benefits. Therefore, investigation is needed to determine if prior exposure to BCMA agents affects BCMA-targeted re-treatment. Here, we use Myeloma Drug Sensitivity Testing (My-DST, Walker et al, Blood Adv. 2020) to compare efficacy of the anti-BCMA bsAb elranatamab from diagnosis to post-CAR-T settings using primary MM samples that include the patients' own T cells. *Methods:* We obtained bone marrow and peripheral blood samples from patients after informed consent and Institutional Review Board approval. Mononuclear cells were incubated with or without elranatamab in triplicate for 48 hours. Flow cytometry measuring MM survival was analyzed with fluorescent antibodies against MM markers CD38, CD138, BCMA, CD46, CD56, CD45, CD19, and CD28, and T cell phenotype using antibodies against CD3, CD4, CD107a, CD107b, CD28, CD38, CD16, CD8, and CD56. To compare patient T cell effectiveness from different timepoints and versus healthy donors (HD), anti-human CD3 MicroBeads and MS columns were used to for T cell isolation. HD or MM patient-derived T cells were then added back to CD3- samples or the H929 MM cell lines and elranatamab My-DST was performed. Viability was normalized to untreated controls with matched source T cells.
Results: Dose response titrations of elranatamab identified a mean EC50 of 52 pM and approximate EC90 of 1nM. The EC90 was used to screen for resistance in 16 primary MM samples, including 9 NDMM, 4 pre-BCMA CAR-T samples and 3 post-BCMA CAR-T *(Fig 1A)*. MM viability of 80% or less was considered the sensitivity threshold, as cytotoxicity beyond this level achieved statistical significance across samples. Across all settings, 87.5% (14/16) met this sensitivity threshold to elranatamab. Notably, 3/3 samples taken from post-CAR-T patients were sensitive. MM cells from all samples tested expressed BCMA. However, 1/2 resistant samples (HTB-1802) had a low E:T ratio. We next examined the impact of T cell source on elranatamab-directed T cell killing of MM. We found that elranatamab treatment led to a greater reduction in primary MM viability when cultured with healthy donor-derived T cells than with MM patient-derived T cells *(Fig 1B)*. Next, we isolated T cells before infusion with CAR-T and after relapse to CAR-T and cultured them with the MM cell line H929 with or without elranatamab. We found no difference in elranatamab-directed cytotoxicity between pre-CAR-T T cells and post-CAR-T T cells, implying T cell health was not adversely affected by CAR-T.
Conclusion: These data demonstrate that My-DST can identify drug resistance to bispecific antibodies with ex vivo cultures that contain the patients' own T cells. The results suggest that most cases of bispecific antibody resistance are due to T cell health or number, rather than low BCMA expression. This supports BCMA-targeted re-treatment in patients with adequate T cell health. Future investigation will aim to further evaluate the critical elements of T cell health with a larger sample size. Ultimately, My-DST has potential as a precision medicine tool to guide bispecific antibody treatment and inform how best to sequence them with CAR-T.

Disclosures Keller: *Pfizer:* Consultancy, Research Funding. **Parzych:** *Pfizer:* Consultancy, Research Funding. **Reiman:** *Pfizer:* Consultancy, Research Funding. **Walker:** *Pfizer:* Consultancy, Research Funding. **Forsberg:** *Bristol-Myers Squibb:* Consultancy; *GlaxoSmithKline:* Consultancy; *Janssen:* Consultancy; *Karyopharm:* Research Funding. **Sherbenou:** *Pfizer:* Consultancy, Research Funding.

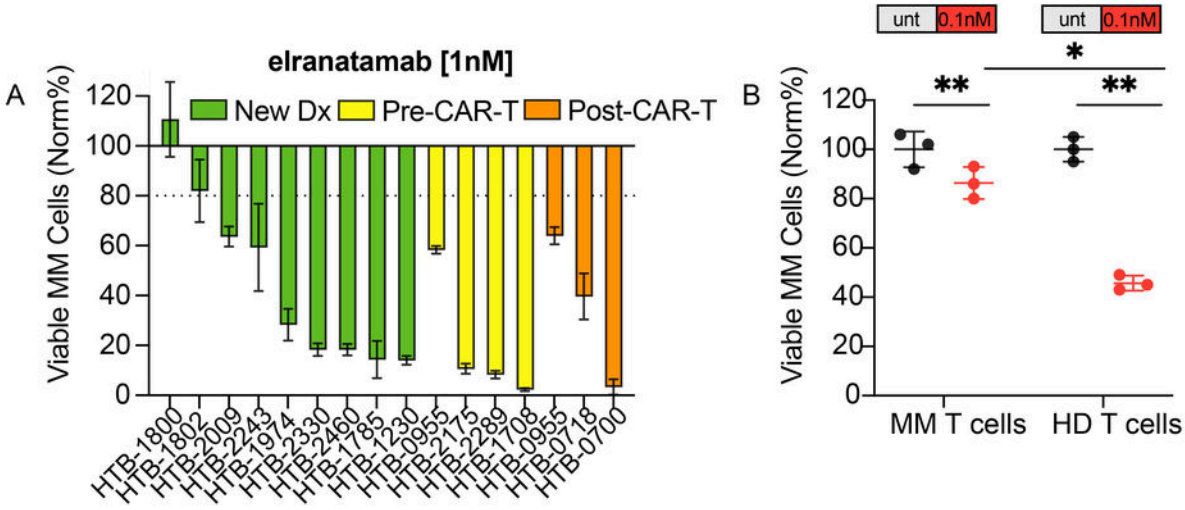

Figure 1. Preclinical activity of elranatamab in primary MM samples
(A) Efficacy of elranatamb (1nM) in 9 NDMM, 4 Pre-CART, and 3 Post-CART primary patient samples after 48 h culture. Dashed horizantal line at 80% indicates cutoff of sensitivity, as all patient samples with sensitivity below this line were statistically significant. (B) Efficacy of elranatamab (0.1nM) cultured with 100,000 MACS sorted CD3- MNCs from HTB-2428 (NDMM) and 80,000 CD3+ T cells from either HTB-2428 or a healthy donor after 48 hr culture. Statistical significance by paired T-test *p-value>0.05, **p-value>0.01.

Figure 1

https://doi.org/10.1182/blood-2023-187385