INCREASED ALEMTUZUMAB EXPOSURE CORRELATES WITH IMPROVED RESPONSES IN HEAVILY PRETREATED R/R ALL PATIENTS: ANALYSIS OF THE BALLI-01 TRIAL

N. JAIN[1], N. BOISSEL[2], A. RAMAKRISHNAN[3], L. POIROT[4], X. NAJ[4], C. FIGLIOLA[4], A. KILCOYNE[4]

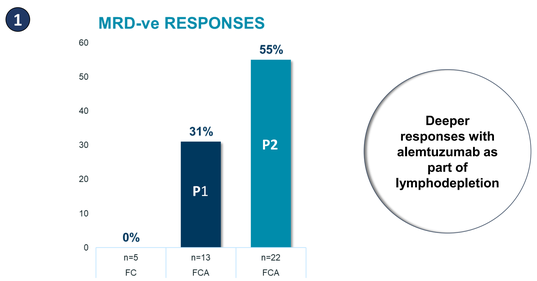
1. University of Texas MD Anderson Cancer Center, Houston, TX, Unites States
2. Hôpital Saint-Louis, Paris, France
3. Sarah Cannon Transplant and Cellular Therapy Program at St. David's South Austin Medical Center, Austin, TX, United States
4. Cellectis Inc, New York, NY, United States

INTRODUCTION

Chimeric Antigen Receptor T-cell (CAR-T) therapy has revolutionized treatment of refractory hematologic cancers, particularly B-cell malignancies. A critical preparative step for CAR-T infusion is lymphodepletion (LD) which creates a more permissive immune environment to improve CAR-T expansion, engraftment and efficacy. Clinical trials across multiple B-cell cancers have demonstrated that the intensity and composition of the LD regimen can significantly influence patient outcomes after CAR-T therapy. In order to optimize the clinical outcome in the allogeneic CAR-T setting, alemtuzumab is being investigated as a means to enhance existing LD regimens. Alemtuzumab is a humanized IgG1 monoclonal antibody directed against CD52, a 21–28 kDa glycoprotein abundantly expressed on most lymphocytes. Alemtuzumab-enhanced lymphodepletion produces a very deep and longer lasting immunosuppressive state. The benefit for CAR-T therapy is a maximally permissive environment for the CAR-T cells to expand. LD regimens with alemtuzumab are currently being investigated in multiple clinical studies including the BALLI-01 study in R/R ALL.

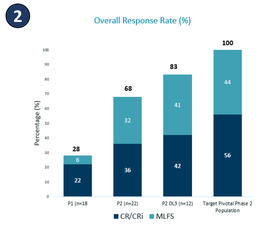
The BALLI-01 study has demonstrated the important role of alemtuzumab in achieving responses. In patients who did not receive this as part of their LD regimes, no MRD-ve responses were observed (Figure 1).

1

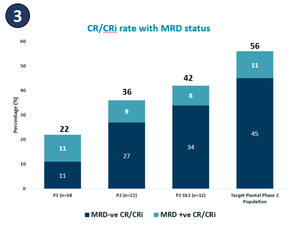


Encouraging response rates were observed in heavily pretreated patients (Median 4-5 prior lines of therapy) with High ORR rates and MRD-ve CR/CRi rates

2



3



Studies have consistently demonstrated that alemtuzumab pharmacokinetics are weight-dependent but there have been no studies to date to understand whether individual exposure to alemtuzumab based on body weight may result in an improved response. This is investigated in the BALLI-01 study.

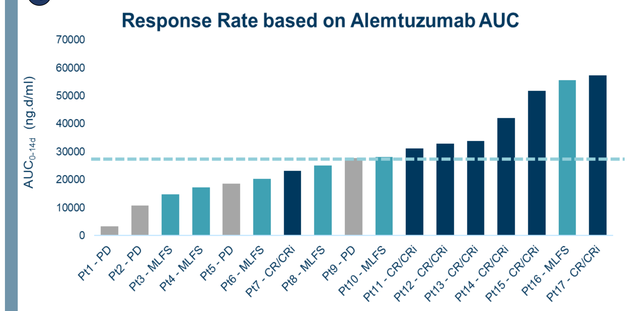
RESULTS

Despite flat dosing, there was significant intersubject variability in alemtuzumab exposure as measured by $AUC_{D0\text{-}14}$. Median overall exposure was 27763 ng.d/mL (range 3279 – 57221 ng.d/mL). A correlation between increased alemtuzumab exposure and improved response was observed. A trend to lower exposure to alemtuzumab was observed in patients with a day 28 response assessment of progressive disease (PD).

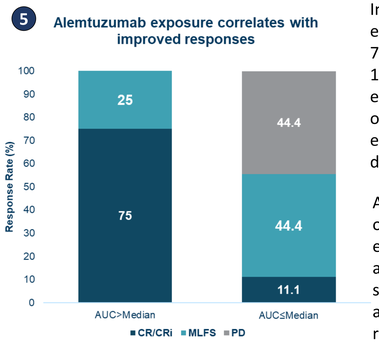
With increased exposure, there was a trend to deepening of response to MLFS and to CR/CRi. There appeared to be a threshold exposure above which the probability of achieving a response assessment of CR/CRi was increased (Figure 4).

By grouping the participants above and below the median AUC, we noted that a higher exposure to Alemtuzumab is associated with an increase in the proportion of CR/CRi.

4



5

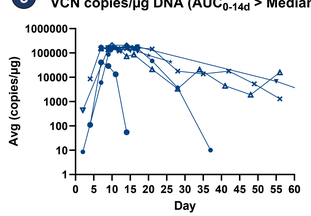


In participants with >median exposure to alemtuzumab, 75% achieved a CR/CRi vs 11.1% in those with ≤median exposure. Additionally, 44.4% of participants with ≤median exposure had progressive disease (Figure 5).

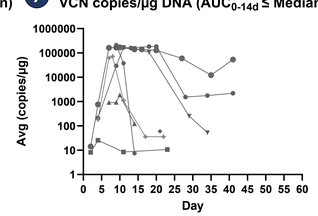
A potential reason for this observation is that lower exposure to alemtuzumab was also associated with lower and shorter lived UCART22 expansion and with earlier host T-cell reconstitution (Figure 6-9).

Reduced UCART22 expansion in participants with lower Alemtuzumab exposure

6

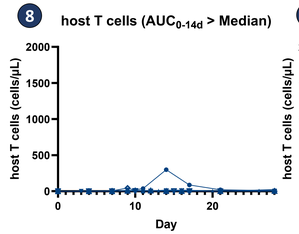


7

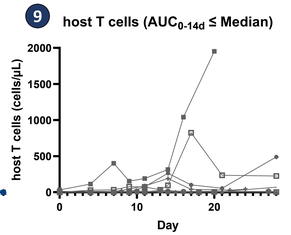


Earlier Host T Cell reconstitution in participants with lower Alemtuzumab exposure

8



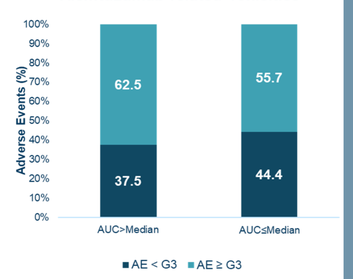
9



No increase in Grade ≥3 toxicities

While there was a trend towards increased efficacy in patients with higher alemtuzumab exposure, this was not associated with a significant increase in Grade ≥3 toxicities

10

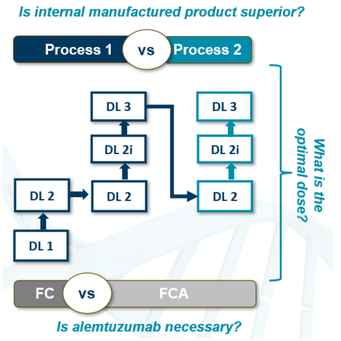


METHODS

BALLI-01 is a first-in-human, open-label, dose escalation and expansion study of UCART22 administered intravenously to patients with relapsed or refractory B-cell Acute Lymphoblastic Leukemia (B-ALL). The purpose of this study is to:

- ❑ Evaluate the safety and clinical activity of UCART22 and determine the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D).
- ❑ Assess the optimal LD regimen (FC vs FCA)
- ❑ Assess whether Internal manufactured product (P2) is superior to externally manufactured product (P1)

Fludarabine, cyclophosphamide (FC) vs. Fludarabine, cyclophosphamide with alemtuzumab (FCA) was investigated as LD regimens (Figure 1). A flat dose of alemtuzumab of 60mg given over 3 days was used. In a cohort of 17 patients, the pharmacokinetic profile of alemtuzumab was analyzed to understand the overall AUC and whether a correlation with CAR-T expansion and response was present. Additionally, the impact of exposure on toxicity was assessed.



CONCLUSIONS

Alemtuzumab is a critical component of the LD regimen in the BALLI-01 trial. For this allogeneic CAR-T therapy, it is important to ensure adequate exposure to alemtuzumab in order to optimize cell expansion and mitigate the risk of early host T cell reconstitution which may compromise response in these heavily pretreated ALL patients with few, if any, alternative treatment options. This increased exposure may be achieved without a significant increase in serious toxicities. Consideration should be given to alemtuzumab dosing regimens, such as weight-based dosing, which reduces intersubject variability in exposure and reduces the risk of underexposure.

ACKNOWLEDGEMENTS

We would like to thank for their participation in the BALLI-01 study Dr. D. DeAngelo, Dana-Farber Cancer Institute, USA; Dr. S. A. Grupp, Children's Hospital of Philadelphia, USA; Dr. R. Larson, University of Chicago, USA; Dr. G. J. Schiller, University of California, Los Angeles, USA; Dr. K. J. Curran, Memorial Sloan Kettering Cancer Center, USA; Dr. J. Cruz, Sarah Cannon –San Antonio Texas Transplant Institute, USA; Dr. L. Mountjoy, Sarah Cannon – Colorado Blood Cancer Institute, USA; Dr. M. Schwartz, University of Colorado, USA; Dr. J.-B. Méar, CHU de Rennes, Rennes, France; Pr. P. Chevallier, CHU Hôtel Dieu, Nantes, France; Dr. M. Balsat, CHU Lyon, Lyon, France; Dr. E. Wang - Roswell Park, Buffalo, NY, USA; Dr. S. Strickland - TriStar Centennial, Nashville, USA; Pr. A. Baruchel - Robert Debre, Paris, France.

Thanks for support in data analysis to A. Duclert, VP in Bioinformatics, Cellectis Paris, France.

CONTACT INFORMATION

xenia.naj@cellectis.com