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704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

A Phase I Clinical Trial of Fully Human Anti-CD19 Chimeric Antigen Receptor T Cells for Relapsed or Refractory Lymphoid Malignancies

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Background:
Chimeric antigen receptor (CAR) T-cells have revolutionized the standard of care for numerous lymphoid malignancies but continue to present challenges related to toxicity, long-term efficacy, cost, and accessibility. Novel CAR-T cell constructs hold promise for improving desired outcomes. CD19 CAR-T cells with fully humanized chimeric antigen receptors have demonstrated excellent preclinical activity and the potential for lower rates of cytokine release syndrome (CRS) and severe immune effector associated neurotoxicity syndrome (ICANS). To evaluate safety, we conducted a phase 1 clinical trial evaluating fully human Hu19-CD841BBZ CAR-T cells with a 4-1BB costimulatory domain against relapsed or refractory (R/R) CD19-positive lymphoid malignancies, utilizing a single lymphodepletion regimen and local CAR-T cell manufacturing using the Prodigy® Device.

Methods:
We designed a parallel-group phase I trial with two clinical groups. Group A enrolled subjects with relapsed and refractory CD19+ lymphomas and chronic lymphocytic leukemia (CLL), while Group B comprised patients with acute lymphoblastic leukemia/lymphoma (ALL). The primary endpoint was safety and toxicity assessment, along with the identification of the recommended phase 2 dose in each clinical group. Secondary endpoints included efficacy evaluation. Dose escalation in each group followed a "3 + 3" phase I study design, with three dose levels: 5e5 CAR-T cells/kg, 1e6 CAR-T cells/kg, and 2e6 CAR-T cells/kg. Lymphodepletion consisted of cyclophosphamide 60mg/kg on day -6 and Fludarabine 25mg/m2/day on days -5 to -3. Dose-limiting toxicities included prolonged CRS grade 3 or higher, ICANS grade $\geq$ 3, and grade $\geq$ 3 non hematologic toxicities with the exception of self-limited (<7 days) laboratory abnormalities without associated symptoms or clinical consequences.

Results:
As of 7/1/2023, a total of 13 patients were enrolled in Group A (NHL), and two patients were enrolled in Group B (B-ALL). Three patients in Group A withdrew consent or were withdrawn at the investigator's discretion due to new comorbid conditions before cell collection. Additionally, three patients were unable to receive CAR-T cell infusions due to disease progression, including two with Burkitt lymphoma. Among the remaining patients, 7 in NHL and 2 in B-ALL, received CART cells. The average age was 59 (range: 40-73), and 2 patients were female. In the NHL group, diseases treated included CLL (3), mantle cell lymphoma (2), follicular lymphoma (1), and Waldenstrom's (1). The median number of prior treatments was 4 (range: 3-10). CAR-T cell product manufacturing was successful in all patients to achieve the target dose, with a mean transduction efficiency of 43.8% (29.7% - 54.6%).
One potential dose-limiting toxicity, nodular regenerative hyperplasia of the liver, considered possibly related to CAR-T cells, was observed in the NHL group at the 1e6 cells/kg dose level, leading to an expansion of this dose level. Other observed toxicities were as expected and manageable. Six patients experienced CRS, with grades 1-2 in the NHL group. Both patients in the B-ALL arm experienced CRS, one grade 1 and one grade e, with observed severity congruent with known disease burden before receiving CAR-T cells. Two cases of CRS required no intervention, while the remaining cases received tocilizumab

(n=4), steroids (n=2), and/or anakinra (n1). There were three occurrences of ICANS, two in Group A and one in Group B. Treatments included corticosteroids (n=3) and anakinra (n=2).

Among the 7 NHL patients evaluable for response, 2 achieved complete remission (follicular, mantel cell), three had a partial response (CLL), and one exhibited stable disease (Waldenstrom's). Two NHL patients (CLL and Mantel Cell) had subsequent disease progression. One B-ALL patient evaluable for response achieved a CR but experienced disease progression at one year and subsequently died.

Discussion:

In this parallel-group phase 1 study, fully human Hu19-CD841BBZ CAR-T cells with a 4-1BB costimulatory domain were successfully manufactured in all patients undergoing leukapheresis. Human CAR-T cells demonstrated preliminary safety and clinical activity in the setting of heavily pre-treated patients with R/R B cell malignancies. A platform of point-of-care manufacture permits access to novel CAR-T cell products, and may facilitate the development of novel immune effector cell products.

Disclosures Deng: *Janssen:* Ended employment in the past 24 months. **Van Besien:** *Hemogenyx:* Consultancy, Current equity holder in publicly-traded company; *Intellia:* Consultancy; *Precision Biosciences:* Research Funding; *Orca:* Research Funding; *Avertix:* Current equity holder in private company; *Calibr:* Research Funding; *BMS:* Research Funding; *Actinium:* Research Funding; *Moprhosys:* Consultancy; *SNIPR:* Consultancy; *Incyte:* Consultancy. **Schneider:** *Lentigen Technology, a Miltenyi Biotec Company:* Current Employment. **Caimi:** *ADC Therapeutics:* Consultancy; *Genentech:* Consultancy; *BMS:* Consultancy; *Lilly Oncology:* Consultancy; *SOBI:* Honoraria; *Novartis:* Consultancy; *Kite Pharma:* Honoraria. **Tomlinson:** *BMS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Chimerics:* Consultancy.

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