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ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

C-CAR039, a Novel Anti-CD20/CD19 Bi-Specific CAR T-Cell Therapy Shows Deep and Durable Clinical Benefits in Patients with Relapsed or Refractory (r/r) B-Cell Non-Hodgkin Lymphoma (B-NHL) in Long Term Follow up

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Background:
We previously reported that C-CAR039, an autologous anti-CD20/CD19 bispecific chimeric antigen receptor (CAR) T-cell therapy, demonstrated a favorable safety profile and promising efficacy in patients (pts) with r/r B-NHL. Of the initial 28 pts treated with C-CAR039 with a median of 3 prior lines of therapy. Only 1 patient experienced grade ≥3 cytokine release syndrome (CRS), and no patient reported grade ≥2 immune effector cell-associated neurotoxicity syndrome (ICANS). The overall response rate (ORR) was at 92.6%, with 85.2% complete response (CR). After a median follow-up of 7 months, 74.1% of pts remained in CR, and the Kaplan-Meier (KM) estimation of progression-free survival (PFS) at 6 months was 83.2%. (Liang et al. ASCO 2021. #2507). Here we present the updated results to include more pts (48 pts) and a longer duration of follow-up (median 23.9 months).

Methods:
This is an open-label, dose escalation and expansion investigator-initiated trial (IIT) of C-CAR039. This trial was conducted at 4 sites to determine the safety and efficacy of C-CAR039 in pts with r/r B-NHL. Pts with r/r diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), follicular lymphoma (FL) or mantle cell lymphoma (MCL) were enrolled and received a single C-CAR039 infusion at a dose of 1.0-5.0x10^6 CAR-T cells/kg after a 3-day conditioning chemotherapy. The primary objective was to assess the safety and tolerability. CRS and ICANS were graded according to ASTCT 2019 criteria. The secondary objectives were to evaluate C-CAR039 efficacy and pharmacokinetics. Response was assessed per Lugano 2014 criteria.

Results:
Between Nov 5, 2019, and Jan 11, 2022, 48 pts received C-CAR039 manufactured using Miltenyi Biotec CliniMACS Prodigy® System. Of the 48 pts, 44 pts had large B-Cell Lymphoma (LBCL) (DLBCL, n = 37; PMBCL, n = 3; tFL, n=4), 3 pts had FL and 1 patient had MCL. The median age was 55 (range, 25-71) years, and 11 (22.9%) pts were ≥ 65 years. Thirty-six (75%) pts were in Ann Arbor Stage III/IV with 3 median prior lines of therapy (range, 1-7). All pts received anti-CD20 antibody and alkylating agents. Eight (16.7%) pts had prior ASCT, 32 (66.7%) pts were refractory to their last treatment, and 22 (45.8%) pts never achieved CR to their prior therapies. Prior to C-CAR039 infusion, 12 (25%) pts received bridging therapy.
As of Jan 15, 2023, 45 pts (93.8%) experienced CRS, of which 44 (91.7%) pts reported grade 1 or 2, only 1 (2.1%) patient experienced grade 3 CRS. Median time to CRS onset was 3 days (range, 1-12), with median duration of 5 days (range, 2-78). Three pts had ICANS at a dose of 5.0x10^6 CAR-T cells/kg, of which 2 were grade 1 and 1 was grade 2. The median time to onset of ICANS was 6 days (range, 5-29), with a median duration of 12 days (range, 3-53). All CRS and ICANS were resolved.

Grade ≥3 neutropenia, anemia, thrombocytopenia and infection were reported in 83.3%, 14.6%, 27.1% and 10.4% of pts, respectively. Second primary malignancy after C-CAR039 infusion were observed in 3 pts; 2 acute myeloid leukemia (AML) occurred at 2 and 10 months, and 1 Epstein-Barr virus-positive cytotoxic T-cell lymphoma was at 8 months, the tumor biopsy was tested with qPCR and CAR transgene was negative and none were related to C-CAR039. Twelve deaths occurred, 9 due to disease progression, 2 due to AE of AML, and 1 due to unknown cause.

Of the 48 pts, 47 pts were evaluable for efficacy (1 patient with DLBCL had no measurable disease at baseline). The ORR and CR rate among evaluable pts were 91.5% and 85.1% respectively. Median time to first response and CR was 1.0 month (range, 0.9-1.9) and 1.1 month (range, 0.9-8.9), respectively. Of the 43 LBCL pts, the ORR was 90.7%, with 86.0% CR. Median DOR, PFS and OS were not reached. The KM estimation of PFS and OS rate at 24 months was 66.0% (95%CI 53.2%-81.9%) and 77.9% (95% CI, 66.6%-91.1%) respectively.

C-CAR039 showed cellular kinetic profile consistent with commercial CAR-T therapies. In 48 evaluable pts, the median T_{max} was 11.5 day (range, 7-31), the median C_{max} was 139,416 copies/g gDNA (range, 708-962,445), and the median $AUC_{0\text{-}28day}$ was 1,513,442 copies/ug•day (range, 3,818-11,594,912.5).

Conclusions:

At a longer median follow-up of 23.9 months, C-CAR039 demonstrated a favorable safety profile with deep and durable response in pts with r/r B-NHL, especially in LBCL pts.

Disclosures Zhu: *Cellular Biomedicine Group Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Huang:** *Cellular Biomedicine Group Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Li:** *Cellular Biomedicine Group Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Zheng:** *Cellular Biomedicine Group Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Lan:** *Cellular Biomedicine Group Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Wan:** *Cellular Biomedicine Group Inc:* Current Employment, Current holder of *stock options* in a privately-held company. **Yao:** *Cellular Biomedicine Group Inc:* Current Employment, Current holder of *stock options* in a privately-held company.

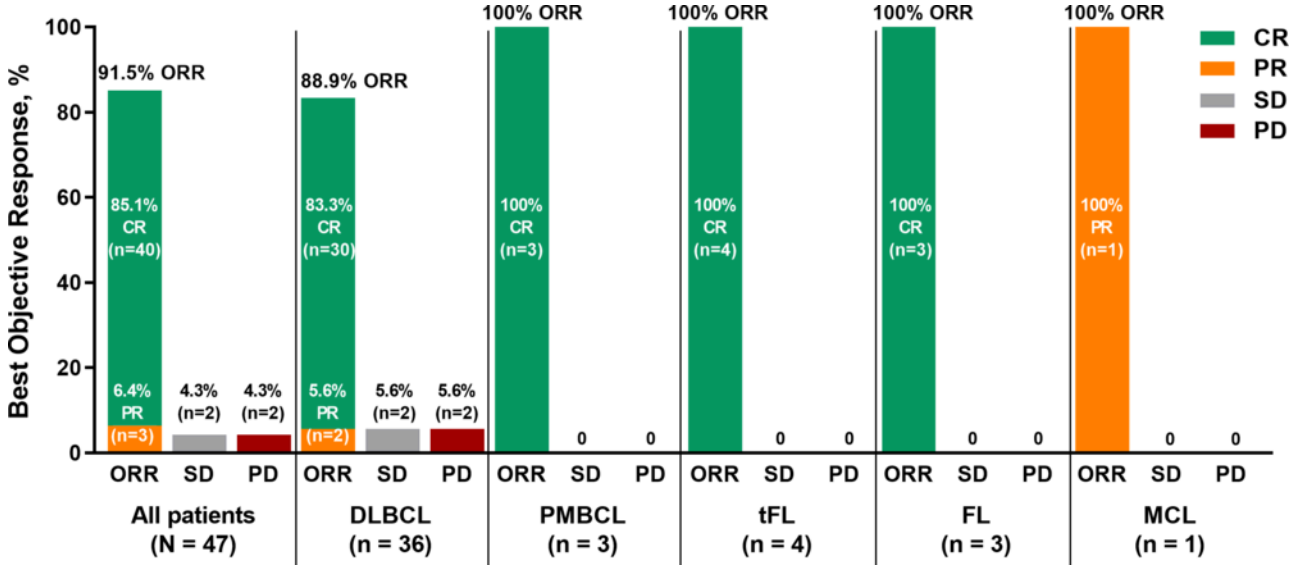

Figure 1

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