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# POSTER ABSTRACTS

## 704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

### Efficacy and Safety of BCMA-Specific CAR T Cell-Based Therapy in Relapsed/Refractory Multiple Myeloma Patients with Extramedullary Disease

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**Background**
Extramedullary disease (EMD) is an aggressive subentity of multiple myeloma (MM), characterized by the ability of a subclone to grow independent of the bone marrow microenvironment, resulting in a high-risk state associated with increased proliferation, evasion of immune surveillance and treatment resistance. Relapsed/refractory multiple myeloma (R/R MM) patients with EMD have unfavorable prognoses and no effective treatment options. B-cell maturation antigen (BCMA)-specific chimeric antigen receptor (CAR) T-cell therapies have shown promising efficacy in R/R MM; however, data on patients with EMD remain limited. We aimed to assess the efficacy and safety of CAR T-cell therapy in R/R MM patients with EMD.

**Methods**
We conducted a retrospective multi-institutional study of 55 R/R MM patients confirmed with EMD at referral. The definition of EMD included (1) soft tissue masses in extraosseous locations resulting from hematogenous spread (EM-E) and (2) bone-related plasmacytomas that extend via disruption of cortical bones into contiguous soft tissues (EM-B). The overall response, long-term outcomes, and safety were assessed. We also characterized differential response between medullary and extramedullary disease, analyzed unique attributes of compartmental toxicity, and explored patterns of relapse in the setting of EMD. Gene expression profiling was performed using nCounter Human CAR-T Characterization Panel (NanoString, #XT-CSO-HCART1-12) on 40 biopsy specimens from patients enrolled in this study, including EMD and bone marrow biopsy specimens at pretreatment or/and at relapse. Results were analyzed based on outcome (no durable response [progression within 6 months, NDR] vs durable response [progression beyond 6 months, DR]). Multiplex immunofluorescence (mIF) was performed for detection of populations and phenotyping of infiltrated CD8 $^{+}$ T cells (Panel A: CD8/PD-1/LAG-3/TIM-3) and macrophages (Panel B: CD68/CD86/CD163) with EMD biopsies.

**Results**
The infusion resulted in an overall response rate of 90.9% (95% confidence interval [CI], 80.4-96.1) in medullary disease and 70.9% (95% CI, 57.9-81.2) in EMD ( $P = 0.008$). Discrepant outcomes between medullary and extramedullary response were observed, with suboptimal and delayed overall response and shortened duration of response achieved in EMD. With a median follow-up of 27.3 months, the median progression-free survival was 8.7 months (95% CI, 3.7-18.8), and the median overall survival was 16.0 months (95% CI, 13.5-20.1). Landmark analysis was conducted to compare OS in patients who progressed versus remained progression-free at the 6-month landmark time point. We demonstrated that progression before 6 months post-infusion is strongly associated with an increased risk of death (HR = 11.15 [95% CI, 3.49 to 35.60]; $P < 0.001$). Local cytokine release syndrome (CRS) was depicted in 21.8% patients and was moderately associated with the occurrence of systemic CRS ($r = 0.322$; $P = 0.017$). 78.2% patients experienced post-infusion progression in EMD, and BCMA $^{+}$ progression constituted the main pattern of EMD progression. At the time of EMD progression, peripheral CAR $^{+}$ cells were detectable, and 50% patients had ongoing documented B cell aplasia. We next interrogated NanoString gene expression data of tumor microenvironment (TME) genes for possible association with clinical response and toxicity. Pretreatment TME enriched for immune checkpoint, and type I interferon signaling were associated negatively with clinical outcomes. We found that the infiltration of type 2 macrophages (CD68 $^{+}$CD163 $^{+}$) in pretreatment TME is associated with the density of activated or exhausted CD8 $^{+}$ T cell ( PD-1 $^{+}$LAG-3 $^{+/-}$), and is associated with no durable response in EMD. We interrogated TME dynamic changes of patients

developing EMD progression between cohorts of DR and NDR. An increase in immune counter-regulatory marker and lower diversity of T-cell receptor (TCR) repertoire, was observed at relapse in cohort of NDR.

**Discussion**

Our study shows that anti-BCMA CAR-T therapy has provided apparent therapeutic advantage over the existing drugs in response rate and long-term survival. Compared with medullary disease, BCMA-specific CAR T cell-based therapy showed limited and discrepant efficacy in EMD, perhaps due to the the properties of EMD-specific microenvironment.

**Disclosures** No relevant conflicts of interest to declare.

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