

Clinical Biomarkers Associated With Progression Free Survival to Ciltacabtagene Autoleucel in Chinese Patients With Relapsed/Refractory Multiple Myeloma From the CARTIFAN-1 Study

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Key Takeaway



In the CARTIFAN-1 study, clinical biomarker data suggest that improved T cell fitness could potentially overcome tumor characteristics of poor prognosis, to enable durable responses to cilta-cel

Conclusions



Longer PFS was associated with higher post-infusion CAR-T peak expansion normalized to sBCMA (surrogate for effector to target ratio). A preferential expansion of CAR+CD8+ T cells was observed



Longer PFS was associated with higher baseline CD8+ naïve T cells, lower baseline sBCMA level, and lower baseline inflammatory biomarkers



Longer PFS was associated with higher baseline lymphocyte counts in patients with autologous stem-cell transplantation as prior treatment



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Poster

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Supplementary material

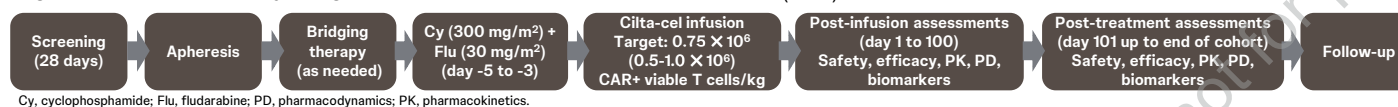
Disclosures

J-Q Mi has no financial conflicts to disclose.

Introduction

- In the pivotal phase 2 CARTIFAN-1 (NCT03758417) study of ciltacabtagene autoleucel (cilta-cel) in Chinese patients (pts), early, deep, and durable responses were demonstrated. A favorable benefit-risk profile was established with a single cilta-cel infusion in heavily pre-treated patients with relapsed/refractory multiple myeloma (RRMM), who received ≥ 3 prior lines of therapy (LOT), including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD)¹
 - With median follow-up of 32.8 months, the overall response rate (ORR) was 87.5% and the median progression free survival (mPFS) was 25.5 months in the first 48 subjects by independent review committee (IRC) assessment²

Figure 1: CARTIFAN-1 study design



Cy, cyclophosphamide; Flu, fludarabine; PD, pharmacodynamics; PK, pharmacokinetics.

Results

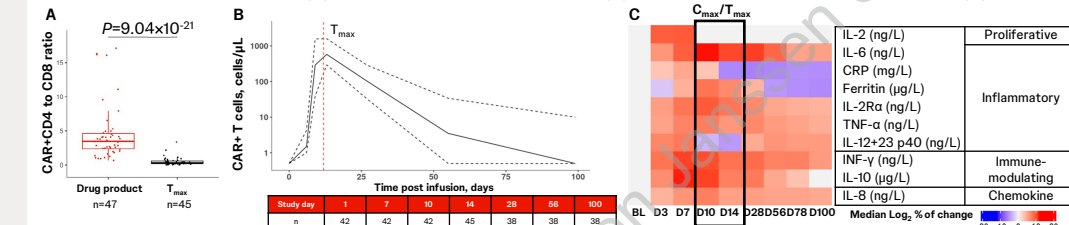
Study population

- As of 07 November 2022, 48 patients were treated with cilta-cel; median follow-up was 32.8 months (range, 0.2-42.8)
- Patients received a median of 4 (range, 3-9) prior LOT. Seventeen (35.4%) patients had prior autologous stem-cell transplantation (ASCT)

Cilta-cel characteristics

- The median CAR+ CD4/CD8 T cell ratio was 3.49 (range: 0.68-17.13) in the drug product and 0.30 (range: 0.03-3.38) at time of cilta-cel peak expansion (T_{max}), indicating a preferential expansion of CAR+CD8+ T cells at T_{max} (Figure 2A)
- CAR+ T cell expansion was variable with a median peak concentration (C_{max}) of 1,182 cells/ μ L (range: 4-8,478 cells/ μ L; N=46) and median T_{max} of 11.90 days (range: 6.73-25.97 days; Figure 2B). Cytokine peak levels commensurate with CAR+ T cell peak expansion (Figure 2C)

Figure 2: CAR+ CD4/CD8 ratio (A), CAR+ T-cell pharmacokinetics (B), and cytokine profiles after treatment (C)

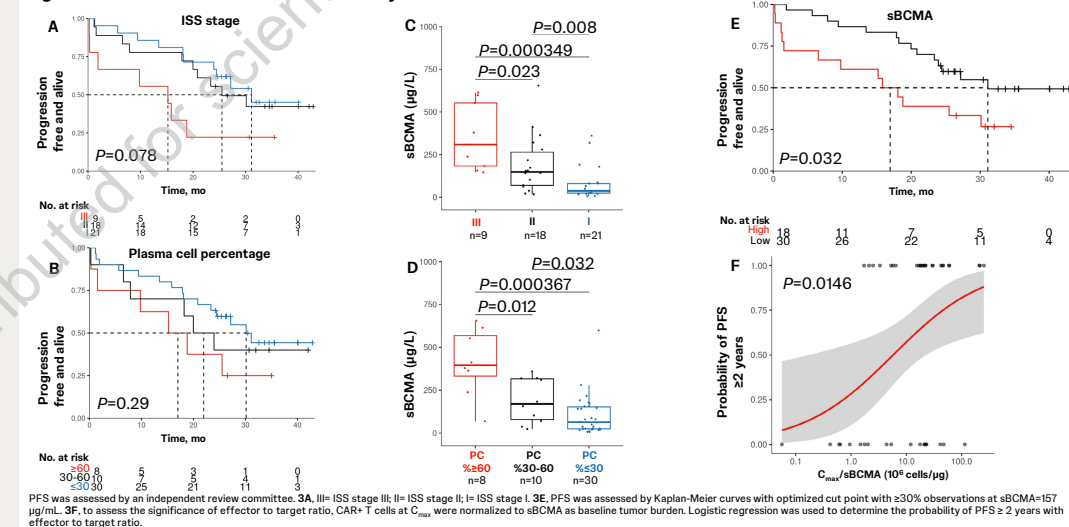


2A, P value determined using Wilcoxon test. 2B, The CAR+ T cells were evaluated at DIAN Diagnostic (Hangzhou, China) using the flow cytometry assay of L.CAR.A panel. Two subjects were excluded from PK analysis due to early death, and one subject has no evaluable C_{max} data. Median is represented by solid gray line; Q1 and Q3 are represented by dashed gray lines. 2C, BL, baseline; D, days post cilta-cel infusion.

Disease intrinsic characteristics and PFS

- ISS stage III and high plasma cell percentage trended to associate with shorter PFS (Figure 3A and 3B)
- Significantly higher levels of soluble BCMA (sBCMA) were observed in pts with ISS stage III (Figure 3C), and pts with plasma cells (PC) $\geq 60\%$ in the bone marrow (Figure 3D). Lower baseline sBCMA was associated with longer PFS (Figure 3E)
- CAR-T peak expansion (C_{max}) was associated with longer PFS when normalized to baseline sBCMA (effector to target ratio, Figure 3F)
- High levels of baseline inflammatory biomarkers (e.g., Ferritin, CRP, IL-10 and IL-6) were associated with shorter PFS (Supplemental Figure 1)

Figure 3: Baseline tumor burden and PFS by CAR+ T cell to sBCMA ratio



PFS was assessed by an independent review committee. 3A, III=ISS stage III; II=ISS stage II; I=ISS stage I. 3E, PFS was assessed by Kaplan-Meier curves with optimized cut point with $\geq 30\%$ observations at sBCMA=157 μ g/mL. 3F, to assess the significance of effector to target ratio, CAR+ T cells at C_{max} were normalized to sBCMA as baseline tumor burden. Logistic regression was used to determine the probability of PFS ≥ 2 years with effector to target ratio.

References

1. Mi J, et al. J Clin Oncol 2023 Feb 20;41(6):1275-1284. 2. Mi J, et al. Presented at CSCO; Sep 21-25, 2023; Xiamen, China.

Objectives

- To evaluate the association of baseline and post-infusion clinical biomarkers with PFS after cilta-cel treatment in RRMM patients at ~ 3 -year follow-up

Methods

Assessments

- Baseline before lymphodepletion and post-infusion whole blood and bone marrow samples and drug products were analyzed by flow cytometry and Meso Scale Discovery (MSD) immunoassays
- High-risk (HR) cytogenetics was assessed at baseline by fluorescence in situ hybridization (FISH) and defined by the presence of del(17p), t(4:14), or t(14:16)

Key eligibility criteria

- RRMM per international Myeloma Working Group criteria
- Eastern Cooperative Oncology Group performance status 0 or 1
- Measurable disease
- ≥ 3 prior LOT, including a PI and an IMiD
- Prior anti-CD38 mAb exposure was not required, as anti-CD38 mAb was not approved in China at the start of the study

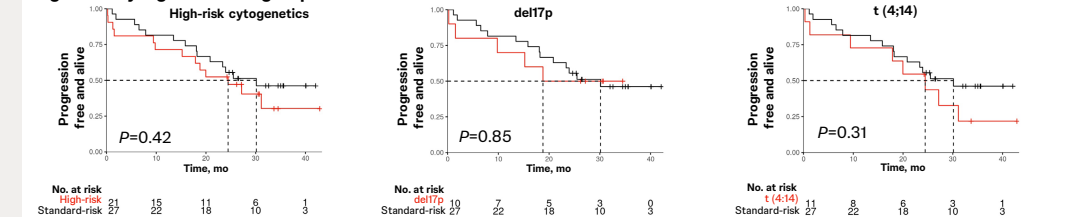
Statistical methodology

- Nonparametric Wilcoxon tests were used for 2-group comparisons
- Kaplan-Meier analysis with log-rank test was used for PFS analysis
- Logistic regression was used to evaluate the relationship between covariate and PFS outcome; analyses are exploratory

HR cytogenetics and PFS

- ORR was 85.7% and 88.9% in HR and standard-risk pts, respectively. A trend towards shorter PFS was observed in pts with HR cytogenetics with no statistical significance (Figure 4)

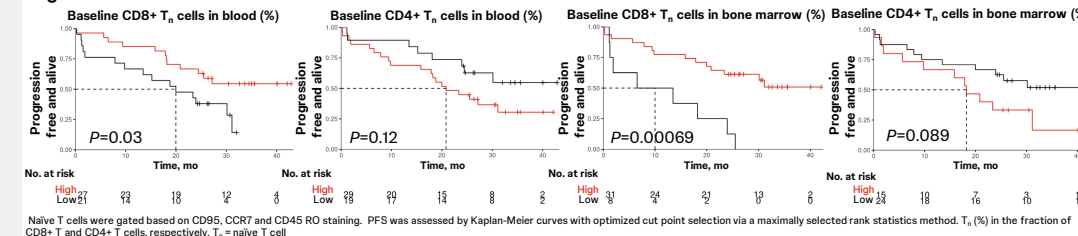
Figure 4: Cytogenetic risk group and PFS



Baseline T cell characteristics and PFS

- Higher baseline CD8+ but not CD4+ naïve T cells in both blood and bone marrow biopspecimens were significantly associated with longer PFS (Figure 5)

Figure 5: Baseline naïve T cells and PFS

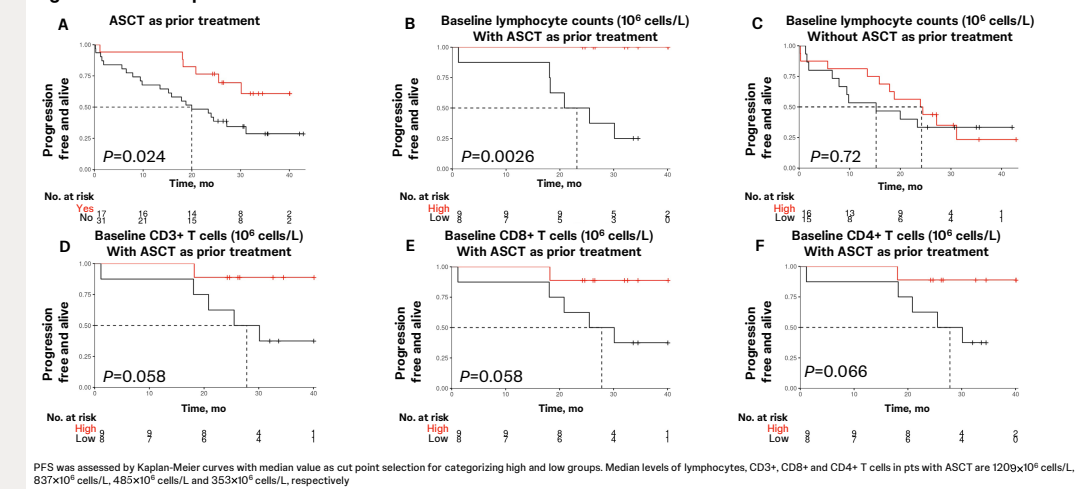


Naïve T cells were gated based on CD95, CCR7 and CD45 RO staining. PFS was assessed by Kaplan-Meier curves with optimized cut point selection via a maximally selected rank statistics method. Tn (%) in the fraction of CD8+ T and CD4+ T cells, respectively. Tn = naïve T cell

Impact of prior autologous stem-cell transplantation (ASCT) treatment on PFS

- In pts with ASCT as prior treatment, PFS was significantly longer compared to pts without ASCT (Figure 6A)
- In pts with ASCT as prior treatment, higher baseline lymphocyte counts significantly associated with even longer PFS, this was not seen in pts without ASCT (Figure 6B and 6C). Higher baseline CD3+, CD8+ and CD4+ T cell counts trended with longer PFS in pts with ASCT as prior treatment (Figure 6D to 6F)

Figure 6: ASCT as prior treatment and PFS



PFS was assessed by Kaplan-Meier curves with median value as cut point selection for categorizing high and low groups. Median levels of lymphocytes, CD3+, CD8+ and CD4+ T cells in pts with ASCT are 1209x10⁶ cells/L, 837x10⁶ cells/L, 485x10⁶ cells/L and 353x10⁶ cells/L, respectively

