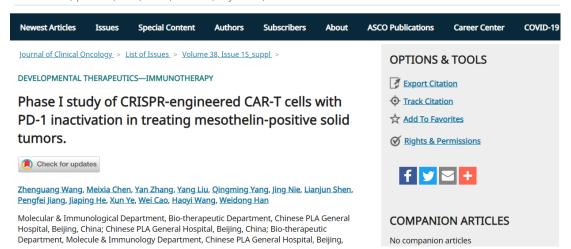
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Abstract

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Background: Our previous phase I study with MPTK-CAR-T (mesothelin-directed 28ζ CAR-T cells with PD-1 and TCR disruption by CRISPR-Cas9 system) demonstrated feasibility and safety of CRISPR-mediated PD-1 inactivation in CAR-T cells, and suggested the natural TCR is beneficial for the proliferation of CAR-T cells in solid tumors. Based on these observations, we initiated a pilot dose escalation study to investigate mesothelin-directed CAR-T cells with only PD-1 disruption by CRISPR (termed as GC008t) in patients with mesothelin-positive advanced solid tumors (NCT03747965). **Methods:** On the data cut-off date (Jan 20, 2020), nine patients (6 pancreatic cancers, 2 ovarian cancers, 1 colorectal cancer) were treated (5 received ≥12 numbers of therapy), three in cohort 1 (0.1-0.2×10⁷/kg), four in cohort 2 (0.5-1.0×10⁷/kg), two in cohort 3 (2.5-5×10⁷/kg). Eight of the 9 patients received lymphodepletion regimen of cyclophosphamide and nab-paclitaxel with or without gemcitabine. Four of the 9 patients received repeat infusions of GC008t per protocol. **Results:** Comparable proliferation capacity was observed *in vitro* between the MPTK-

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CAR-T and the GC008t products. The mean PD-1 surface expression in cell products was 0.5% (range, 0.2%-0.9%). GC008t infusions were well tolerated with no observed on-target/off-tumor toxicity, autoimmune activity. Only two patients in cohort 3 developed grade 1 CRS with fever and rash. Circulating GC008t expanded with a peak at day 7-14 and became undetectable by qPCR beyond 1 month. The mean peak levels of circulating CAR-T cells between GC008t and MPTK-CAR-T at similar dose level were not statistically significant. Failure of GC008t engraftment after repeat infusion was observed in 2 out of 4 $\,$ patients. The best response of the 7 evaluable patients was stable disease in 4 $\,$ and partial response in 2 patients (dosed $\geq 1 \times 10^7 / \text{kg}$) with PFS of 80 and 160 days. Conclusions: Phase I trial of GC008t further establishes that genetic inactivation of PD-1 in CAR-T cells by CRISPR is feasible and safe. The expansion and persistence of CAR-T cells with PD-1 disruption is not improved significantly even in the setting of natural TCR and lymphodepletion. Future endeavors are needed to improve the clinical efficacy of CAR-T therapy in the treatment of $\ensuremath{\mathsf{CAR-T}}$ solid tumor. Clinical trial information: NCT03747965 ☑.

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