Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

DEVELOPMENTAL THERAPEUTICS—IMMUNOTHERAPY

Phase I study of CRISPR-engineered CAR-T cells with PD-1 inactivation in treating mesothelin-positive solid tumors.

Zhenguang Wang, Meixia Chen, Yan Zhang, Yang Liu, Qingming Yang, Jing Nie, Lianjun Shen, Pengfei Jiang, Jiaping He, Xun Ye, Wei Cao, Haoyi Wang, Weidong Han

Molecular & Immunological Department, Bio-therapeutic Department, Chinese PLA General Hospital, Beijing, China; Chinese PLA General Hospital, Beijing, China; Bio-therapeutic Department, Molecule & Immunology Department, Chinese PLA General Hospital, Beijing, China; Gracell Biotechnologies (Shanghai) Co., Ltd, Shanghai, China; State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China

Show Less

Abstract Disclosures

Abstract

3038

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 ($0.1\text{-}0.2\times10^7$/kg), four in cohort 2 ($0.5\text{-}1.0\times10^7$/kg), two in cohort 3 ($2.5\text{-}5\times10^7$/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-

OPTIONS & TOOLS

Export Citation
Track Citation
Add To Favorites
Rights & Permissions

COMPANION ARTICLES

No companion articles

ARTICLE CITATION

DOI: 10.1200/JCO.2020.38.15_suppl.3038
Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 3038-3038.

Published online May 25, 2020.

WHAT'S POPULAR

Most Read | Most Cited

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline
Brahmer et al.

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update
Key et al.

Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2–, Node-Positive, High-Risk, Early Breast Cancer (monarchE)
Johnston et al.

Prognostic Index for Acute- and Lymphoma-Type Adult T-Cell

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 ≥ 1×10^7/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 solid tumor. Clinical trial information: NCT03747965.

Leukemia/Lymphoma
Katsuya et al.

Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer
Gadgeel et al.