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First-in-human phase I study of TCR-T therapy targeting KRAS G12V in metastatic solid tumors

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Background

About 10% of colorectal cancers (CRC) and 30% of pancreatic cancers (PC) harbor the KRAS p.G12V mutation, a critical driver of tumorigenesis. To date, no clinical data have been reported for TCR-engineered T cell therapies targeting this mutation. NW-301V is a novel TCR-T therapy composed of autologous T cells transduced with a naturally selected TCR specific for the KRAS p.G12V neoantigen presented by HLA-A*11:01. In addition, NW-301V T cells co-express the CD8αβ co-receptor to further enhance functionality. Here, we present initial findings from the first-in-human, investigator-initiated phase 1 study of NW-301V in patients (pts) with metastatic CRC and PC.

Methods

The study uses a modified 3+3 design with 3 dose levels (DLs): 3e8 (2-5e8), 1.5e9 (1-4e9) and 7.5e9 (5-12e9) transduced CD8 T cells. Pts undergo apheresis for NW-301V manufacture, and lymphodepletion (LD) with fludarabine (30mg/m^2/day) and cyclophosphamide (500mg/m^2/day) for 3 days, prior to NW-301V infusion. Low-dose IL-2 (500,000 IU) is administered s.c. twice a day for 10 days post infusion. Primary objectives are to assess the safety, tolerability, and determine MTD and RP2D. Secondary objectives include evaluating PK and preliminary efficacy.

Results

As of Feb 28th, 2025, DL1 and DL2 enrollment have completed. 8 pts (median age 57 yrs) have been treated, including 4 at DL1 (all PCs) and 4 at DL2 (all CRCs). The pts had received a median of 3 prior systemic therapies. NW-301V was well tolerated with most adverse events being hematological toxicities related to LD. Two pts had Grade 1-2 CRS. No ICANS, DLTs, or deaths have been observed. According to RECIST 1.1, the best overall responses were evaluated as PR in 3 pts (1 PC at DL1 and 2 CRCs at DL2), SD in 2 pts (both CRC at DL2) and PD in 3 pts (all PCs at DL1). Overall response rate was 37.5% (3/8) across both DLs and 50% (2/4) at DL2. Disease control rate was 62.5% (5/8) across both DLs and 100% (4/4) at DL2. In 2 pts, responses deepened from SD at week 4 to PR at week 8. All PRs and SDs lasted >3 months.

Conclusions

Initial results confirm that NW-301V demonstrates a favorable safety profile and promising anti-tumor activity in KRAS G12V-mutated PCs and CRCs. Ongoing dose escalation aims to further assess anti-tumor efficacy at higher doses and establish the RP2D.

Legal entity responsible for the study

The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.

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Disclosure

R. Liu, J. Fang, Z. Cai: Financial Interests, Personal, Full or part-time Employment: Neowise Biotechnology; Financial Interests, Personal, Stocks or ownership: Neowise Biotechnology. S. Zhong, D. An, S. Peng: Financial Interests, Personal, Full or part-time Employment: Neowise Biotechnology; Financial Interests, Personal, Stocks or ownership: Neowise Biotechnology; Financial Interests, Personal, Leadership Role: Neowise Biotechnology. All other authors have declared no conflicts of interest.