

PRELIMINARY SAFETY AND EFFICACY OF AUTOLOGOUS ANTI-MSLN T CELL ENGAGER-LOADED T CELLS (CAB-T) IN PATIENTS WITH MESOTHELIN-EXPRESSING ADVANCED SOLID TUMORS

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Background Mesothelin (MSLN) is highly expressed in various solid tumor types with low levels of expression in some normal healthy tissues. Our CAB-T platform is a novel, proprietary T cell based anti-CD3 bispecific T cell engager (TCE) delivery system. Our preclinical studies indicated its superior anti-tumor efficacy over traditional 2nd-generation CAR-T formats. Here, we report the preliminary safety and efficacy of MSLN-targeting CAB-T (MSLN-CAB-T) in patients with MSLN-expressing advanced solid tumors during an investigator-initiated trial (IIT).

Methods This is an open-label, single-center study with an accelerated dose titration followed by a 3+3 design. Patients were enrolled with MSLN+ advanced or metastatic solid tumors (detected by IHC; 2+/3+ $\geq 30\%$ in viable tumor cells). MSLN-CAB-T cells were manufactured using autologous PBMC that were freshly isolated from leukapheresis. Following lymphodepletion, MSLN-CAB-T cells were administered intravenously followed by safety and efficacy observations, and the detection of MSLN-CAB-T expansion and cytokine/TCE levels in patient sera. Primary objectives included safety and tolerability to determine the maximum tolerated dose (MTD). Secondary objectives included overall safety, preliminary efficacy, and PK.

Results From Apr, 2021 to Nov, 2021, seven patients had enrolled (4, ovarian cancer; 1, colon cancer; 2, duodenal carcinoma). 4/7 received ≥ 4 prior lines of therapy, 2/7 received anti-PD1 treatment. Dose levels included 3×10^5 cells/kg (n=1); 1×10^6 cells/kg (n=1); 3×10^6 cells/kg (n=3); 5×10^6 cells/kg (n=1), and 1×10^7 cells/kg (n=1). There were no dose-limiting toxicities (DLT) or treatment-related deaths. Treatment-related adverse events (TRAEs) of \geq Grade 3 were reported in two patients (1×10^6 cells/kg and 1×10^7 cells/kg). Grade 1 cytokine release syndrome (CRS) was reported in all of the patients $\geq 3 \times 10^6$ cells/kg and only one patient dosed at 1×10^7 cells/kg developed Grade 3 CRS (quickly recovered after treatment with corticosteroid and tocilizumab). Post-infusion, MSLN-CAB-T expansion peaked in peripheral blood within 5–19 days. In five evaluable patients (4, ovarian cancer; 1, colon cancer), the best overall response was stable disease (n=1); two ovarian cancer patients dosed at 3×10^6 cells/kg showed tumor shrinkage with one patient whose tumor reduced in size of $\sim 26.89\%$ at the first assessment. Dose-dependent PK and TCE levels correlated with MSLN positivity and tumor burden.

Conclusions MSLN-CAB-T showed good preliminary safety in subjects with MSLN+ solid tumors, and MTD has not yet been reached. This provides the rationale to expand the study, especially for patients with tumors expressing higher levels of MSLN ($\geq 60\%$ in viable tumor cells) as a monotherapy or in combination with other agents.

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Ethics Approval Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

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