691 **FIRST-IN-HUMAN TRIAL OF NOVEL HBSAG-SPECIFIC TCR T CELL THERAPY (SCG101) IN PATIENTS WITH HBV-RELATED HEPATOCELLULAR CARCINOMA**

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Background Hepatitis B virus (HBV) infection accounts for 75–80% of virus-associated Hepatocellular carcinoma (HCC). HBV DNA integration into the host cell genome produces viral antigens and can lead to tumorigenesis, which can be effectively targeted by HBsAg-specific TCR-T cells. SCG101, a first-in-class autologous HBsAg-specific TCR-T cell therapy, has demonstrated high affinity, avidity, and profound antiviral and antitumor functionalities in preclinical studies. This abstract presents the evaluation of SCG101 in subjects with HBV-related HCC in an investigator-initiated trial.

Methods The trial enrolled six subjects with advanced HBV-related HCC, HBsAg(+), HBeAg(-), BCLC B/C stage, and HLA-A*02:01 allele, who had received one to three prior systemic therapies and at least 12 months of antiviral treatment (Entecavir and/or Tenofovir). All subjects received a single dose of $5x10^7$ or $1x10^8$ cells/kg SCG101 intravenously after lymphodepletion. Safety, pharmacokinetics (PK), antiviral, and antitumor activities were evaluated.

Results Following infusion, transferred T cells exhibited significant dose-dependent proliferation and demonstrated strong persistence during the study period. SCG101 infusion resulted in a profound antiviral and/or antitumor activities in all six subjects. Serum HBsAg dropped in all six subjects, with four out of six experiencing a reduction of >1 log. Transient ALT elevation correlating with HBsAg reduction was observed in all subjects, indicating the killing of target cells in the liver. Disease control was observed in all subjects (4/4, 100%) with >1 log serum HBsAg reduction, including two partial responses (one cPR and one uPR, according to mRECIST and iRECIST) and two stable diseases (SD). Patients without significant (>1 log) serum HBsAg reduction showed no tumor response. Until data cut-off, the medium progression-free survival (mPFS) was 11 months compared to 0.7 months in subjects with and without >1 log serum HBsAg reduction, respectively. The treatment was well-tolerated, with no dose-limiting toxicity or neurotoxicity reported.

Conclusions SCG101, as a single agent, demonstrated significant antiviral and antitumor activity in subjects with HBV-related HCC. The persistence of TCR^+ T cells, reduction of serum HBsAg, and tumor response are strongly correlated with the mechanism of action of SCG101. A phase I/II clinical trial to further evaluate the safety and efficacy of SCG101 is ongoing.

Ethics Approval This study was approved by Peking Union Medical College institution's Ethics Board with approval number HS-2780, Zhongshan Hospital institution's Ethics Board with approval number B2021–342, The First Hospital of China Medical University institution's Ethics Board with approval number 2021–266, and The Sixth People's Hospital of Shenyang institution's Ethics Board with approval number 2020-X003–01.

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