

Highlights from ASCO 2021

CAR-T Cell Therapy – Eyeing Opportunities in Solid Tumors

ASCO 2021

CAR-T cell therapy has transformed the treatment of B-cell lymphoma and multiple myeloma. Translating these results to solid tumors is challenging due to several barriers such as lack of appropriate therapeutic targets, tumor heterogeneity, and a suppressive solid tumor microenvironment (TME). AACR 2021 highlighted preclinical evidence on innovative CAR-T strategies that address some of these challenges.¹⁻³ At ASCO 2021, preliminary data was presented showcasing some of these approaches in solid tumors.

Improving antigen targeting

Many tumor antigens found in solid tumors lack specificity and are often found at low levels in normal tissue. In the absence of the tumor antigen specificity, the risk of significant on-target off-tumor toxicity is remarkably augmented.

First-in-human studies focused on several solid tumor associated target antigens, such as MUC-1 and GPC3, with preliminary data presented.

1. MUC-1 (Solid Tumors)

The cancer-associated MUC-1 (TnMUC1) is hypoglycosylated, compared to the heavily glycosylated form found in normal cells, so it can be specifically targeted by CAR-T cells without on-target off-tumor effect.⁴

- Phase I dose escalation study of CART-TnMUC1-Cells is ongoing for the treatment of MUC-1 expressing solid tumors (resistant ovarian cancer, pancreatic cancer, TNBC, or NSCLC).⁴ The preliminary data reported CAR-T expansion in all patients and SD in all patients in one of the cohorts (cohort 2). No evidence of safety concerns or on-target/off-tumor toxicity was reported.
- Another Phase I study is evaluating the safety of adoptively transferred autologous T cells genetically modified to express huMNC2-CAR44 in patients with metastatic MUC1* positive breast cancer. Dose escalation phase is completed and three expansion cohorts are planned in luminal, HER2 positive, and TNBC.⁵ Data is awaited.

2. GPC3 (Hepatocellular Carcinoma)

GPC3 is highly expressed in hepatocellular carcinoma (HCC) and is a promising target for HCC. Preclinical studies have shown that fourth-generation CAR-GPC3 T cells co-expressing a transcription factor more effectively killed GPC3+ HCC xenografts.⁶

- First-in-human Phase I trial of autologous CAR-GPC3 T cells for GPC3+ heavily pretreated advanced HCC includes cohorts evaluating CAR-T cells in combination with TKIs and PD-1/L1 inhibitors. The CAR-t/TKI combination demonstrated an ORR of 16.7% and DCR of 50%. The mPFS was 4.2 months.⁶ No treatment-related death or neurotoxicity was reported. The most common \geq grade 3 AE was hematological toxicity, which was reversible. CRS reported was manageable.⁶

Modulating the immunosuppressive solid tumor microenvironment

Phase I study design for solid tumor associated target antigens such as MMP2 and HER2 was described.

1. HER2 (HER2-expressing Solid Tumors)

CAR macrophages reprogram the solid TME and present neoantigens to T cells, leading to epitope spreading and immune memory.

- CAR macrophage product CT-0508 expressing an anti-HER2 CAR is in a Phase I study and will enroll ~18 patients in HER2 expressing heavily pretreated locally advanced (unresectable) or metastatic solid tumors. Patients will be enrolled in two groups (Group 1: split dosing between Day 1, Day 3, and Day 5; Group 2: full dose on Day 1).⁷ Data is awaited.

2. MMP2 (Glioblastoma)

Chlorotoxin CAR-T (CLTX CAR-T) cells uniquely utilize chlorotoxin (CLTX), a peptide component of scorpion venom, as the tumor-targeting component of the CAR. Strong CLTX and CLTX cells binding to tumor cells were reported in the majority of primary GBM lines. Anti-tumor activity was also demonstrated against glioblastoma while not exhibiting any off-tumor recognition of normal cells and tissues, indicating a potentially optimal safety and efficacy profile.

- A Phase I study is currently enrolling patients with MMP2+ recurrent or progressive glioblastoma.⁸

Key questions:

1. Will approaches such as CAR-macrophages drive success of CAR-T cell therapy in solid tumors?
2. How will target antigen specificity play a role in optimizing CAR-T cell efficacy in solid tumors?
3. Will combinations be a better approach? If so, which combinations will be synergized rather than being an additive with CAR-T cells in solid tumors?

References:

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SmartAnalyst is helping clients interpret the data presented at ASCO 2021 (June 4-8) focusing on key developments in cancer research.

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