Novel T cell receptor therapy shows early anti-tumor activity

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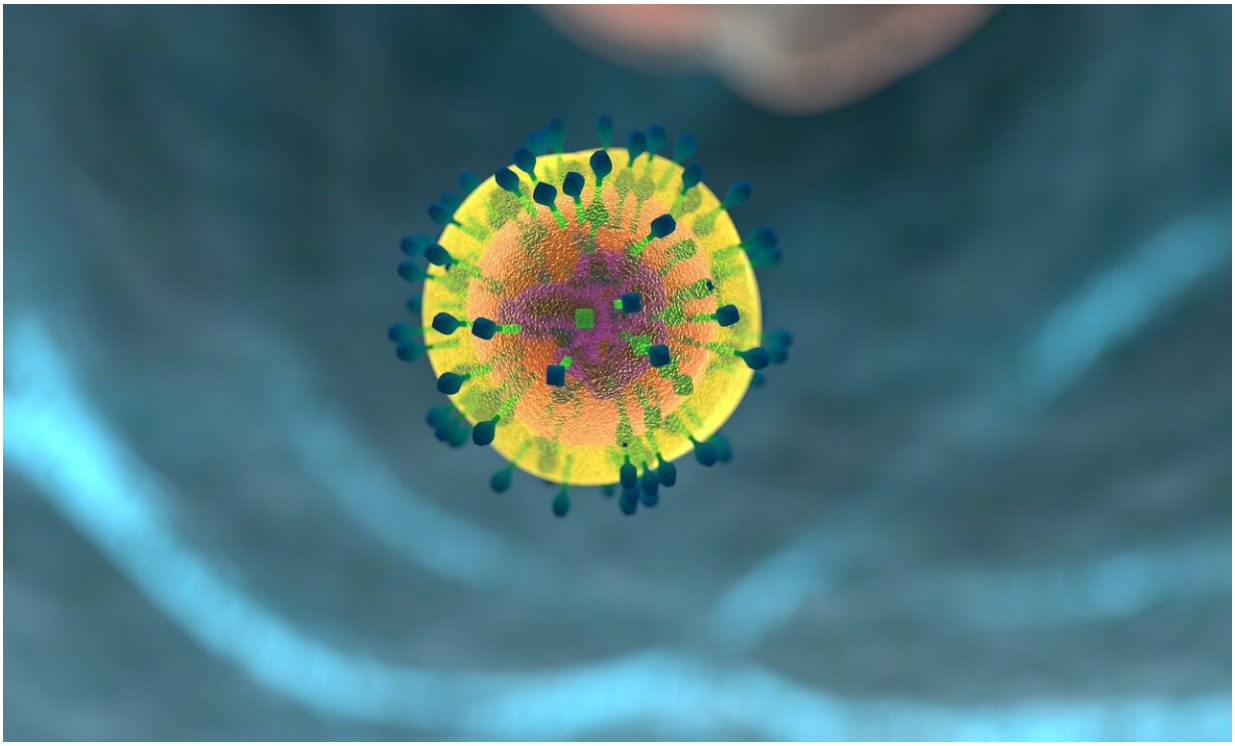

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Afamitresgene autoleucel (afami-cel; formerly ADP-A2M4), an adoptive T cell receptor (TCR) therapy targeting the MAGE-A4 cancer antigen, achieved clinically significant results for patients with multiple solid tumor types in a Phase I clinical trial led by researchers at The University of Texas MD Anderson Cancer Center.

The outcomes, published today in Nature Medicine, were especially noteworthy in the subgroup of patients with synovial sarcoma, where afami-cel achieved an objective response rate of 44% compared to the overall response rate of 24% across all cancer types. Initial data from this trial were presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting.

According to principal investigator David S. Hong, M.D., professor of Investigational Cancer Therapeutics, these early results demonstrate a proof-of-concept for this novel cell therapy approach in solid tumors.

"These high response rates are significant because patients with synovial sarcoma really have very few options after high-dose chemotherapy with ifosfamide," Hong said. "The overall toxicity from afami-cel was manageable, and we saw evidence of early activity in other cancer types. These results suggest this is an approach with the potential to work in solid tumors where there are currently no approved cellular therapies."

The goal of TCR therapies is to more accurately target solid tumor cells without the toxicities to normal cells often associated with chimeric antigen receptor (CAR)-based cell therapies. Unlike CAR-based cell therapies, which recognize designated surface proteins, TCR therapies like afami-cel can target proteins normally found inside the cell. Using the T cell's native receptor, TCR therapies can recognize protein fragments—in this case from MAGE-A4—bound to immune-related proteins on the cell surface.

A total of 38 patients were treated with afami-cel on the study, with an average of three prior lines of therapy. Participants were 58% male; 92% of participants were white and the rest were Asian. The study included 16 patients with synovial sarcoma, nine with ovarian cancer, three with head and neck cancer, two each with esophageal cancer, non-small cell lung cancer, urothelial cancer and myxoid/round cell liposarcoma, and

one each with gastric cancer and melanoma.

All patients experienced treatment-related adverse events, with low blood cell counts (lymphopenia, leukopenia, neutropenia, anemia and thrombocytopenia) the most common. Prolonged cytopenia persisting at four weeks after afami-cel treatment occurred in 17 patients (45%). Two patients had trial-related deaths, which resulted in the lowering of the maximum age at screening and discontinued use of the high-dose cyclophosphamide lymphodepletion regimen.

The median duration of response was 26 weeks across all patients and 28 weeks in the synovial sarcoma subgroup. These results in synovial sarcoma led to an ongoing Phase II trial of afami-cel for patients with advanced synovial sarcoma or myxoid/round cell liposarcoma that also is being led by MD Anderson.

Early results of afami-cel led to another Phase I trial, also led by Hong, evaluating the next generation of afami-cel, known as ADP-A2M4CD8. This new TCR therapy expresses a CD8 co-receptor with the goal of broadening the immune response in solid tumors. Hong shared encouraging early data from that trial at the European Society for Medical Oncology (ESMO) Congress 2022.

These trials are part of an ongoing strategic alliance between MD Anderson and Adaptimmune, which aims to expedite the development of novel T cell therapies in multiple cancer types.

More information: David Hong, Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial, *Nature Medicine* (2023). DOI: 10.1038/s41591-022-02128-z. www.nature.com/articles/s41591-022-02128-z

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