STUDENT CORNER-
LETTER TO THE EDITOR

New frontier of gene therapy: Tecelra's promise for metastatic synovial sarcoma

Hammad Amjad[1], Muhammad Farhan[2], Mobeen Abid[3]

Dear Editor, Synovial sarcoma (SS) is a sporadic, invasive soft tissue sarcoma with epithelial differentiation, primarily affecting young adults and adolescents. It constitutes about 10% of soft tissue sarcomas. The five-year survival rate for SS is 50% to 60%, and five-year metastasis-free survival rate is 40% to 60%. It grows slowly, which can delay diagnosis, and often metastasises to the lungs. Patients clinically present with a deep, multinodular mass that has been present for years, accompanied by local pain and tenderness. However, symptoms vary upon tumour location. Magnetic resonance imaging is preferred for diagnosis and staging; however, Positron emission tomography/Computed tomography scans are also used to check for metastases.[1] Current treatments include surgery for localised tumours, radiotherapy and more generally standard treatment is anthracycline-based chemotherapy. At the same time, clinical trials on engineered T-cell receptor gene therapy for either confirmation or testing have taken place and are still ongoing.[2] Gene therapy involves the transfer of a genetic material into patient's cells and works by either enabling or inhibiting expression of the target gene or by modifying it. In contrast, chemotherapy effectively kills or inhibits cancer cells and possesses the ability to destroy healthy cells, making it nonspecific and with grave side effects such as immunosuppression. Until recently, the FDA has approved Tecelra with the active agent, afamitresgene autoleucel (afami-cel), a one-of-a-kind first-ever gene therapy for metastatic SS.[3] It consists of the patient's own human leukocyte antigen-restricted autologous T cells engineered to express a receptor with enhanced affinity and specificity for the MAGE-A4 peptide. This antigen triggers the immune system and is expressed by the tumour cells in SS. Phase I trial conducted with the primary objective of evaluating the safety, tolerability and clinical activity of afami-cel revealed that, out of 16 pre-treated metastatic SS patients, seven partially responded to afami-cel infusion representing an overall response rate (ORR) of 44%. At the same time eight showed stable disease resulting in 94% disease control rate. Two patients also exhibited significant reduction of pleural metastases, with one patient achieving complete resolution of a pleural metastasis. The sustained decrease in the size of target lesions over several months in some patients after a single infusion of afami-cel indicates that its anti-cancer effects last for a greater period than expected after a single cycle of lymphodepletion (LD) chemotherapy. In addition, the secondary endpoints exceeds the historically low ORRs reported for current standard-of-care treatments, such as pazopanib and trabectedin, used in post-first-line metastatic setting.[4] Phase II trial conducted to analyse the safety and efficacy of afami-cel reported an ORR of 39% with 17 patients showing partial response and progression-free survival of 3.8 months in the 44 pre-treated patients with SS without any treatment-related deaths. The survival probability for patients was estimated to be 90% at 12 months and 70% at 24 months. The common adverse effects (AEs) included cytopenias, nausea, fatigue, pyrexia, anaemia, and cytokine release syndrome, being the AE of special interest.[5] The trials establish Tecelra as a promising breakthrough in the treatment of patients with metastatic or unresectable SS with prior LD chemotherapy and demonstrate the effectiveness of T-cell receptor therapy in targetting cancer antigens of solid tumours, supporting the expansion of this strategy to other solid malignancies, however, long-term efficacy, safety and durability of afami-cel remain areas of continued investigation. Even though the findings showed better toleration of afami-cel, indicating a promising therapy, more trials with a larger population size of patients should be conducted.

[1,3]4th Year MBBS Student, Karachi Medical and Dental College, Karachi, Pakistan.[2]5th Year MBBS Student, Karachi Medical and Dental College, Karachi, Pakistan.

Correspondence: Hammad Amjad. **Email:** hammu4954@gmail.com

ORCID ID: 0009-0008-1602-2147

Submission complete: 18-09-2024 **First Revision received:** 21-12-2024

Acceptance: 25-01-2025 **Last Revision received:** 24-01-2025

DOI: https://doi.org/10.47391/JPMA.22180

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Mangla A, Gasalberti DP. Synovial Cell Sarcoma. Treasure Island, FL: StatPearls Publishing; 2025.
2. Fuchs JR, Schulte BC, Fuchs JW, Agulnik M. Emerging targeted and cellular therapies in the treatment of advanced and metastatic synovial sarcoma. Front Oncol 2023;13:e1123464. doi: 10.3389/fonc.2023.1123464.
3. Otto MA. Stern V. FDA Approves First Engineered Cell Therapy for a Solid Tumor. [Online] 2024 [Cited 2024 August 28]. Available from URL: https://www.medscape.com/viewarticle/fda-approves-first-engineered-cell-therapy-solid-tumor-2024a1000eb2?orm=fpf.
4. Hong DS, Van Tine BA, Biswas S, McAlpine C, Johnson ML, Olszanski AJ, et al. Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial. Nat Med 2023;29:104-14. doi: 10.1038/s41591-022-02128-z.
5. D'Angelo SP, Araujo DM, Abdul Razak AR, Agulnik M, Attia S, Blay JY, et al. Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial. Lancet 2024;403:1460-71. doi: 10.1016/S0140-6736(24)00319-2.

AUTHORS' CONTRIBUTIONS:
HA: Paraphrasing.
MF: Topic and paraphrasing.
MA: Literature search on different sites i.e Pubmed, Google Scholar etc, extracted the relevant data and drafting.