T-Cell Receptor T-Cell (TCR T) Therapy

Clinical Guidelines

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Guideline Application

For medical necessity clinical coverage criteria for Medicare Advantage plans, refer first to the Medicare Coverage Database for NCDs and LCDs/LCAs, then the Medicare Benefit Policy Coverage Manual.

Background

Adoptive cell therapy (ACT) uses genetically engineered human lymphocytes and is increasingly being investigated in patients with hematologic malignancies and solid tumors. Two approaches to ACT include chimeric antigen receptor (CAR) T-cell therapy which uses an artificial receptor introduced into the immune effector cells to recognize tumor cell surface antigens and T-cell receptor (TCR)-based adoptive therapy which uses genetically modified lymphocytes that are directed against specific tumor markers. TCR-based therapy involves patient screening, leukapheresis, generation of transduced TCR product, lymphodepletion, and infusion of the TCR-based product. The challenges of TCR-based therapy include those associated with product manufacturing, patient selection, and preparation with lymphodepletion. TCR-based therapy is increasingly being investigated in the treatment of solid tumors due to its ability to recognize tumor-specific epitopes presented by the major histocompatibility complex (MHC) molecules on the tumor cell surface. This strategy has a potentially broader applicability as there are far more tumor-specific sequences within a cell and presented in the MHC than there are tumor-specific proteins on the surface. These intracellular cancer targets are only accessible by TCR-based approaches and not by CAR-based approaches (Tsimberidou et al., 2021). In principle, ACT can use a variety of effector cells, but it is most commonly based on T-cells or natural killer (NK) cells derived from the patient and genetically modified. Most immunotherapies fail because they are unable to deliver an effective pool of anti-tumor effector cells and/or because the effector cells mobilized are inhibited by tumor-associated factors. TCR-based therapy delivers a functional pool of cells through the ex vivo manufacture of activated lymphocytes with known selectivity and potency (Ping et al., 2018).

FDA-Approved Agents

Afamitresgene autoleucel (Tecelra®) is a melanoma-associated antigen A4 (MAGE-A4)-directed genetically modified autologous T cell immunotherapy approved on August 02, 2024, for the treatment of adults with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices. The indication was approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. On June 17, 2026, the FDA approved Tecelra for the treatment of adults and pediatric patients ≥ 12 years of age with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices. This expanded age indication represents a transition from FDA accelerated approval to traditional (full) approval.

Universal Minimum Eligibility Requirements

Along with disease indications, the patient's performance status and comorbidities are critical considerations for adoptive cell therapies including TCR-T cell therapy. Eligibility evaluation should consider the following:

- Renal function (GFR, Cr)
- Liver function (AST/ALT, bilirubin)
- Cardiac status (LVEF)
- Pulmonary status (dyspnea, pulse ox)
- Hematologic status (ANC< ALC, platelets)
- Baseline neurologic examination and evaluation
- Presence of autoimmune conditions and use of immunosuppressive agents
- Presence of active or uncontrolled infection

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Universal Contraindications

The following are considered contraindications for TCR-T cell therapy:

- Pregnancy
- Members receiving immunosuppressive therapy for an autoimmune disorder
- Any active, uncontrolled infection
- Uncontrolled human immunodeficiency virus (HIV) infection. These patients should be under the management of an HIV specialist and their disease controlled prior to TCR T-cell therapy
- Hepatitis B or C infection
- Hematologic malignancies

Indications

Synovial sarcoma

Synovial sarcoma (SS) is a mesenchymal tumor with partial epithelial differentiation. It is commonly seen in older children and younger adults. The presence of t(X;18)(p11.2;q11.2) is a pathognomonic feature of synovial sarcoma. Synovial sarcoma is the most well-established 'translocation-associated sarcoma,' and several molecular techniques are used to determine this translocation. It is a very aggressive malignancy with high potential for metastasis. Patients with extremity synovial sarcoma usually present with a painless, deep-seated mass. Although the cause of synovial sarcoma is not yet clearly defined, tumor cells in more than 90% of patients have a translocation involving chromosome 18 and chromosome X. Like other soft-tissue sarcomas (STS), surgical resection (to achieve microscopic negative margins) along with perioperative radiotherapy remains the cornerstone of treatment. The role of neoadjuvant or adjuvant chemotherapy remains controversial in adults but is utilized regularly in the pediatric population. Synovial sarcoma accounts for up to 10% of all STS. In the US, 800 - 1000 new cases of SS are diagnosed annually. According to an analysis of the Surveillance, Epidemiology, and End Results (SEER) database study, the age-adjusted incidence rate of SS in the US is 0.177 per 100,000 (approximately 580 incident cases) with a prevalence rate of 0.65 per 100,000 (approximately 2129 prevalent cases). Although SS can affect any age, it is known to occur more commonly in adolescents and adults younger than 30. SS is considered the most common sarcoma in the adolescent age group (Mangla and Gassalberti, 2023).

Treatment

Afamitresgene autoleucel (Tecelra®)

Tecelra (afamitresgene autoleucel) is a melanoma-associated antigen A4 (MAGE-A4)-directed genetically modified autologous T cell immunotherapy product consisting of CD4- and CD8-positive T cells transduced with a self-inactivating lentiviral vector (LV) expressing an affinity-enhanced T cell receptor (TCR) specific for the human MAGE-A4. Autologous T cells transduced with MAGE-A4-c1032 LV express the affinity-enhanced TCR on the cell surface. The TCR recognizes an HLA-A*02 restricted MAGE-A4 peptide. MAGE-A4 is an intracellular cancer-testis antigen that has restricted expression in normal tissues and is expressed in synovial sarcoma. Antigen-specific activation of Tecelra via TCR-peptide-HLA-A*02 complex results in T cell proliferation, cytokine secretion, and killing of MAGE-A4/HLA-A*02 expressing synovial sarcoma cells (FDA, 2024).

D'Angelo and colleagues (2024) reported the results of the investigational cohort (cohort 1) of the SPEARHEAD-1 trial, an open-label, multi-center, non-randomized, phase 2 trial that enrolled HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P, and HLA-A*02:06P allele positive patients with inoperable or metastatic synovial sarcoma who had received prior systemic therapy with either doxorubicin and/or ifosfamide and whose tumor expressed the MAGE-A4 tumor antigen. The study included patients with measurable disease according to RECIST v1.1, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and glomerular filtration rate (GFR) ≥ 60 mL/min. The study excluded patients with HLA-A*02:05P in either allele, patients on systemic corticosteroids for at least 14 days prior to leukapheresis and lymphodepletion, and recipients of allogeneic hematopoietic stem cell transplants. Patients underwent high resolution HLA typing at a centralized testing site and had tumor samples tested for MAGE-A4

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expression by an immunohistochemistry (IHC) clinical trial assay at a centralized testing site. Patients underwent leukapheresis for collection of autologous cells for processing and manufacture into Tecelra. Risk of manufacturing or delivery failure was 8% in the clinical trial (4/52) patients. Lymphodepleting chemotherapy consisted of fludarabine 30 mg/m^2/day for 4 days (Day -7 to Day -4) and cyclophosphamide 600mg/m^2/day for 3 days (Day -7 to Day -5). Patients with GFR 60- 79 mL/min received an adjusted fludarabine dose of 20 mg/m^2/day. Tecelra was administered as a single intravenous (IV) infusion on Day 1.

Fifty-two (52) patients with cytogenetically confirmed synovial sarcoma (n=44) and myxoid round cell liposarcoma (n=8) were enrolled and received afami-cel in cohort 1. Patients were heavily pretreated (median number of prior lines of systemic therapies was 3; range: 1 to 12 lines). Prior therapies included ifosfamide (100%), doxorubicin (95%), pazopanib (48%), trabectedin (25%), dacarbazine (11%), and gemcitabine (11%). Median follow up time was 32.6 months (IQR 29.4-36.1). At data cutoff (August 30, 2023), 11 patients were ongoing in long-term follow up and 6 were ongoing in the interventional phase. Between leukapheresis and initiation of lymphodepletion, 20 (38%) of 52 patients received bridging therapy. The most commonly used bridging therapy was pazopanib (69%). The median dose of Tecelra was 8x10^9 MAGE-A4 TCR-positive T cells (range: 2.68 x 10^9 to 9.99 x10^9). In the modified intent-to-treat population, the overall response rate was 37% (19 of 52 patients; 95% CI 24-51) with all 19 patients having a best overall response of partial response. The overall response rate (ORR) was 39% (17 of 44 patients; 95% CI 24-55) in patients with synovial sarcoma and 25% (2 of 8 patients; 95% CI 3-65) in patients with myxoid round cell liposarcoma. Median time to initial conformed response was 4.9 weeks (95% CI 4.3-8.1) in patients with a response. Median duration of response (DOR) was 11.6 months (95% CI 4.4-18.0) in patients with synovial sarcoma and 4.2 months (95% CI 2.9-5.5) in patients with myxoid round cell liposarcoma. Higher response rates were observed in patients with synovial sarcoma who were female, had higher MAGE-A4 expression, had lower disease burden before lymphodepletion (sum of longest diameters of target lesions <100 mm), or did not have bridging therapy.

All 52 patients who received afami-cel had treatment-emergent adverse events. Cytopenias were the most common grade 3 or worse adverse events: lymphopenia occurred in 50 (96%) patients, neutropenia in 44 (85%), and leukopenia in 42 (81%). Ten (19%) patients experienced prolonged cytopenia, defined as grade 3 or worse cytopenia at week 4 after T-cell infusion, including 5 (10%) patients with neutropenia, four (8%) with anemia, and three (6%) with thrombocytopenia.

Cytokine release syndrome (CRS) events were mostly grade 1-2, however one (2%) of 52 patients had a grade 3 event. Serious events occurred in five (10%) patients. CRS occurred in both the synovial sarcoma and myxoid round cell liposarcoma groups early after afami-cel infusion, with a median time to onset of two days and resolution in a median of three days. CRS was managed with supportive care and 19 (37%) patients received tocilizumab; two of the 19 patients required corticosteroids, and all cases resolved.

No treatment-related deaths occurred, and no deaths occurred in the 30 days after afami-cel infusion. All 28 deaths in the cohort were attributed to disease progression by the investigators. Of these 28 deaths, 4 occurred in the interventional phase and 24 occurred in the long-term follow up, over the range of 66-875 days after T cell infusion. There were no detected occurrences of replication-competent lentivirus or secondary malignancies.

Trial limitations include the single-arm, non-randomized design which doesn’t permit the conclusion that afami-cel is superior to systemic agents for refractory synovial sarcoma and myxoid round cell liposarcoma. A randomized trial, however, would be difficult to conduct for several reasons: no globally consistent second-line therapy exists for these patients, so selecting a comparator would be challenging, and HLA*A-02 typing and MAGE-A4 expression requirements would entail selection of subsets of these two very rare cancers, for which according to de Pinieux et al. (2121) the estimated incidence is 1.55 per million people per year for myxoid round cell liposarcoma and 1.67 per million people per year for synovial sarcoma.

On June 17, 2026, the FDA approved Tecelra for the treatment of adults and pediatric patients ≥ 12 years of age with unresectable or metastatic synovial sarcoma who have received prior chemotherapy, are HLA-A*02:01P-, HLA-A*02:02P-, HLA-A*02:03P-, or HLA-A*02:06P-positive and whose tumor expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices. Tecelra was previously approved in August

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2024 for this indication in adults only. The approval of Tecelra for the expanded indication was based on the expanded efficacy population from the SPEARHEAD-1 trial. The evaluable efficacy population included 137 patients. The major efficacy measure was ORR. DOR was an additional outcome measure. In the efficacy evaluable population, the ORR was 43.8% (95% CI, 35.3 to 52.5). The median DOR was 5.3 months (95% CI, 4.5 to 8.2). Approximately one-third of responders maintained responses ≥ 24 months. (FDA, 2026).

NCCN recommends Tecelra as palliative treatment as a single agent (useful in certain circumstances) as subsequent lines of therapy for advanced/metastatic disease with disseminated metastases (synovial sarcomas only) and HLA-A*02:01P, HLA-A*02:02P, HLA-A*02:03P or HLA-A*02:06P positive and whose tumor expresses the MAGE-A4 antigen (NCCN Compendium®; NCCN Soft Tissue Sarcoma V5.2026).

Afamitresgene autoleucel (Tecelra®) is considered medically necessary in adults and pediatric patients ≥ 12 years of age with unresectable or metastatic cytogenetic-confirmed synovial sarcoma who meet the following criteria:

- Documentation of prior chemotherapy regimen containing either anthracycline or ifosfamide
- Has measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST). To view RECIST The Radiology Assistant: RECIST 1.1 - the basics
- Documentation of HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive **AND**
- Tumor sample expresses the MAGE-A4 antigen as determined by FDA-approved or cleared companion diagnostic devices
- Documentation of Eastern Oncology Cooperative Group (ECOG) performance status ≤ 1
- Therapy will be administered at a manufacturer-accredited treatment center. Locate an authorized treatment center here https://www.tecelra.com/hcp/authorized-treatment-center

Afamitresgene autoleucel (Tecelra®) is considered unproven in patients who do not meet all of the above criteria.

Afamitresgene autoleucel (Tecelra®) is contraindicated in patients positive for HLA-A*02:05 allele.

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Review and Approval History

Date	Description
08/16/2024	New clinical guideline.
08/28/2024	Review by Optum Hematopoietic Stem Cell Transplantation and Cellular Therapy Expert Panel.
09/09/2024	Approved by Optum Clinical Guideline Advisory Committee.
09/18/2024	Approved by Pharmacy and Therapeutics (P&T) Committee.
10/03/2024	Approved by Medical Technology and Assessment Committee (MTAC).
12/04/2025	Annual Review. No substantive changes. Approved by Medical Technology and Assessment Committee (MTAC).
12/08/2025	Annual Review. No substantive changes. Approved by Optum Clinical Guideline Advisory Committee.
12/10/2025	Annual Review. No substantive changes. Approved by Medicare Advantage Policy and Technology Assessment Committee (MAP TAC).
12/17/2025	Annual Review. No substantive changes. Approved by Pharmacy and Therapeutics (P&T) Committee.
09/14/2026	Annual Review: Extended afamitresgene autoleucel (Tecelra®) indication from adults only to adults and pediatric patients ≥ 12 years of age. Approved by Optum Clinical Guideline Advisory Committee.
09/16/2026	Annual Review: Extended afamitresgene autoleucel (Tecelra®) indication from adults only to adults and pediatric patients ≥ 12 years of age. Approved by Pharmacy and Therapeutics (P&T) Committee.
10/01/2026	Annual Review: Extended afamitresgene autoleucel (Tecelra®) indication from adults only to adults and pediatric patients ≥ 12 years of age. Approved by Medical Technology and Assessment Committee (MTAC).
10/14/2026	Annual Review: Extended afamitresgene autoleucel (Tecelra®) indication from adults only to adults and pediatric patients ≥ 12 years of age. Approved by Medicare Advantage Policy and Technology Assessment Committee (MAP TAC).

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