What Is CAR-T Cell Therapy? Mechanism, Approved Indications, and Key Evidence

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> CAR-T cell therapy engineers a patient's own T lymphocytes to express chimeric antigen receptors (CARs) that recognise and destroy tumour-specific targets. Six products are now FDA- and EMA-approved across haematological malignancies. This article explains the manufacturing process, approved indications, landmark efficacy data, and the clinical management of cytokine release syndrome and neurotoxicity.

KEY TAKEAWAYS

- CAR-T therapy uses a patient's own T cells, genetically engineered with a CAR construct targeting a tumour antigen, expanded ex vivo, and reinfused
- Six FDA/EMA-approved products target CD19 (B-cell malignancies) or BCMA (multiple myeloma); no solid tumour products are currently approved
- ZUMA-1 showed 58% CR in relapsed/refractory DLBCL; CARTITUDE-1 showed 97.9% ORR in heavily pre-treated multiple myeloma
- CRS affects 70-95% of patients; Grade 3+ managed with tocilizumab and corticosteroids within the first 14 days
- Referral to a CAR-T-certified centre is required for manufacturing logistics and specialised toxicity monitoring

What Is CAR-T Cell Therapy?

CAR-T cell therapy is a form of adoptive cell immunotherapy in which a patient's own T lymphocytes are genetically engineered to express chimeric antigen receptors (CARs) targeting tumour-specific surface proteins.4 The modified cells are expanded ex vivo and reinfused into the patient, where they mount a directed anti-tumour response. Unlike conventional chemotherapy or checkpoint inhibitors, CAR-T therapy delivers a living drug that can persist and proliferate in the body.

How Does It Work?

The manufacturing process involves three steps: leukapheresis to collect T cells from peripheral blood, transduction using a viral vector (typically lentiviral or retroviral) to insert the CAR gene, and ex vivo expansion before infusion.1 The CAR construct consists of an extracellular antigen-binding domain derived from a monoclonal antibody, a transmembrane linker, and intracellular co-stimulatory and activation domains (CD28 or 4-1BB, plus CD3-zeta). Upon binding to the target antigen, the CAR activates the T cell and triggers cytotoxic killing.

Before infusion, patients receive lymphodepleting chemotherapy, typically fludarabine plus cyclophosphamide, to reduce regulatory T cells, create cytokine space, and improve CAR-T engraftment.3

Approved Indications

As of 2026, six CAR-T products have received regulatory approval from the FDA and/or EMA, all targeting haematological malignancies:

ProductTargetApproved IndicationTisagenlecleucel (Kymriah)CD19Paediatric/young adult ALL; DLBCLAxicabtagene ciloleucel (Yescarta)CD19DLBCL, follicular lymphoma, PMBCLBrexucabtagene autoleucel (Tecartus)CD19Mantle cell lymphoma; B-ALLLisocabtagene maraleucel (Breyanzi)CD19DLBCL; CLL/SLLIdecabtagene vicleucel (Abecma)BCMARelapsed/refractory multiple myelomaCiltacabtagene autoleucel (Carvykti)BCMARelapsed/refractory multiple myelomaNo CAR-T products are currently approved for solid tumours, though trials are ongoing in glioblastoma, pancreatic cancer, and non-small cell lung cancer.

Key Efficacy Data

For large B-cell lymphoma, axicabtagene ciloleucel (ZUMA-1) demonstrated a complete response rate of 58% at median follow-up of 15.4 months, establishing CAR-T as a viable third-line option.1 The ZUMA-7 trial demonstrated superiority over standard second-line chemoimmunotherapy in early-relapsed DLBCL, with event-free survival of 8.3 months versus 2.0 months.2

For multiple myeloma, ciltacabtagene autoleucel (CARTITUDE-1) showed an overall response rate of 97.9% in heavily pre-treated patients, with a complete response rate of 78.6% at median follow-up of 27.7 months.3

Safety: CRS and ICANS

The two most clinically significant toxicities are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).5 CRS occurs in 70 to 95% of patients across approved products. Grade 3 or higher CRS occurs in approximately 10 to 30% of cases and is managed with tocilizumab and corticosteroids. ICANS affects approximately 30 to 60% of patients and can manifest as encephalopathy, aphasia, or cerebral oedema in severe cases. Both toxicities typically occur within the first 14 days after infusion and are manageable at experienced centres.

Clinical Takeaway

CAR-T cell therapy offers durable remissions in patients with relapsed or refractory haematological malignancies who have exhausted conventional options. Referral to a CAR-T-certified treatment centre is required in most jurisdictions due to the complexity of manufacturing logistics and specialised toxicity management protocols.

Future Directions and Challenges

While CAR-T cell therapy has revolutionised the treatment of certain haematological cancers, several challenges and areas for future development remain. One significant hurdle is the high cost of therapy, which can exceed $400,000 per patient, posing a substantial burden on healthcare systems. Efforts are underway to reduce manufacturing costs and streamline the production process, including the development of allogeneic "off-the-shelf" CAR-T products derived from healthy donors, which could offer greater accessibility and reduce the vein-to-infusion time.

Another key area of research focuses on expanding CAR-T therapy to solid tumours. The tumour microenvironment

in solid cancers presents unique challenges, including antigen heterogeneity, immunosuppressive factors, and physical barriers to T-cell infiltration. Strategies being explored include targeting multiple antigens, engineering CAR-T cells to resist immunosuppression, and combining CAR-T therapy with other modalities such as oncolytic viruses or checkpoint inhibitors. Furthermore, ongoing research aims to mitigate toxicities like CRS and ICANS, potentially through novel CAR designs or prophylactic interventions, to improve the overall safety profile of these life-saving therapies.

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