

T-Cell–Based Therapies for B-Cell Lymphomas: A Summary Resource

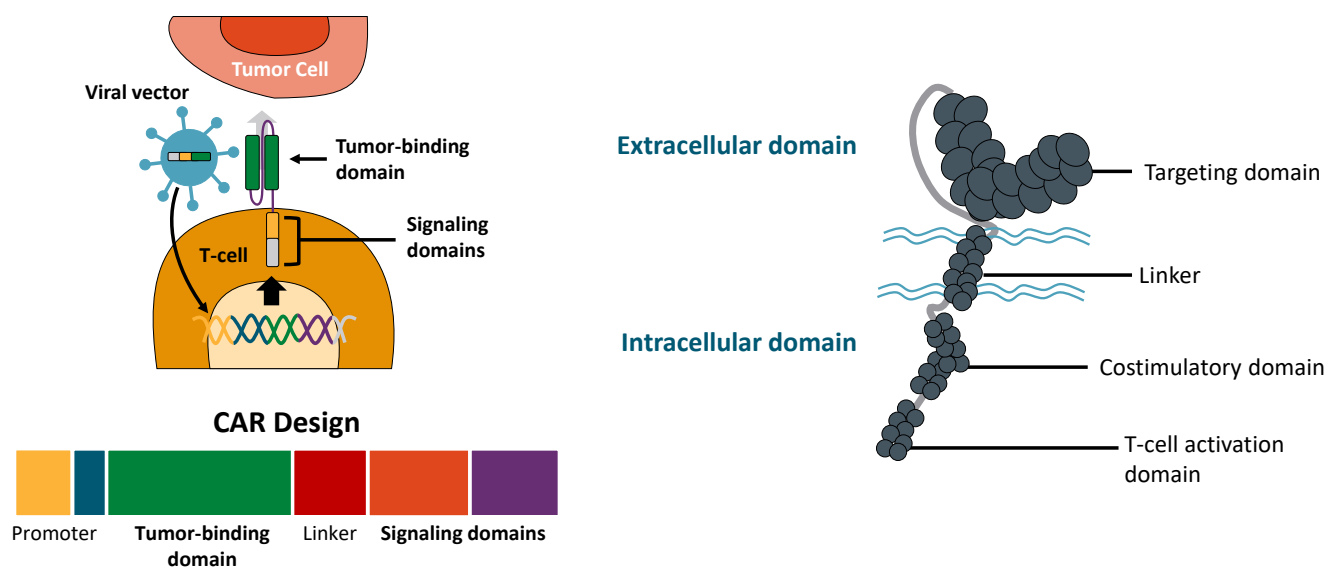


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Mechanism of Action and Molecular Targets

- CAR T-cell therapy consists of T-cells genetically modified to express a T-cell receptor targeting a specific antigen expressed on malignant cells¹
 - Upon binding to the target antigen, the CAR T-cell activates and kills the target cell
 - As of December 2021, all FDA-approved CAR T-cell therapies for patients with lymphomas use modified autologous T-cells, although therapies are under investigation using allogeneic T-cells²⁻⁵

General Schematic for CAR T-Cells⁶



- Tabelecleucel is an off-the-shelf allogeneic T-cell immunotherapy that consists of EBV-specific T-cells created by co-culturing transformed donor EBV–antigen presenting cells with donor T-cells to select for and expand EBV-directed cytotoxic T-cells
 - EBV-directed T-cells, with diverse HLA profiles intended to cover 95% of patients, are ready in advance of patient need and are individually selected for each patient based on appropriate HLA restriction and allele profile

Indications and Recommendations for Use of T-Cell Therapy in B-Cell Lymphomas

- The autologous CAR T-cell therapies currently approved for lymphomas (as of December 2021) target cancer cells expressing CD19
- The investigational allogeneic T-cell therapy tabelecleucel targets cancer cells positive for Epstein-Barr virus (EBV)

FDA-Approved CAR T-Cell Therapy Targeting CD19	Indications and Recommendations
Axicabtagene ciloleucel ²	FDA-approved indications: • Adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from FL, primary mediastinal large B-cell lymphoma, and high-grade B-cell lymphoma (not indicated for primary CNS lymphoma) • Adults with R/R FL after ≥2 lines of systemic therapy (accelerated approval) NCCN guidelines recommends axicabtagene ciloleucel for⁷: • Patients with grade 1/2 FL after ≥2 lines of systemic therapy, including ≥1 anthracycline or anthracenedione-based regimen (unless contraindicated) • Patients with histologic transformation to DLBCL from either grade 1/2 FL or nodal marginal zone lymphoma, after ≥2 prior chemoimmunotherapy regimens, including ≥1 anthracycline or anthracenedione-based regimen (unless contraindicated) • Patients with DLBCL after ≥2 prior chemoimmunotherapy regimens
Brexucabtagene autoleucel ³	FDA-approved indications: • Adults with R/R MCL (accelerated approval) • Adults with R/R B-cell precursor ALL NCCN guidelines recommends brexucabtagene autoleucel for⁷: • Third-line treatment of MCL after chemoimmunotherapy and BTK inhibitor
Lisocabtagene maraleucel ⁴	FDA-approved indications: • Adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL NOS (including DLBCL arising from indolent lymphoma), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and follicular lymphoma grade 3B (not indicated for primary CNS lymphoma) NCCN guidelines recommends lisocabtagene maraleucel for⁷: • Patients with histologic transformation to DLBCL from either grade 1/2 FL or nodal marginal zone lymphoma, after ≥2 prior chemoimmunotherapy regimens, including ≥1 anthracycline or anthracenedione-based regimen (unless contraindicated) • Patients with DLBCL after ≥2 prior chemoimmunotherapy regimens
Tisagenlecleucel ⁵	FDA-approved indications: • Patients aged 25 years or younger with B-cell precursor ALL that is refractory or at least second relapse • Adults with R/R large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from FL, and high-grade B-cell lymphoma (not indicated for primary CNS lymphoma) NCCN guidelines recommends tisagenlecleucel for⁷: • Patients with histologic transformation to DLBCL from either grade 1/2 FL or nodal marginal zone lymphoma, after ≥2 prior chemoimmunotherapy regimens, including ≥1 anthracycline or anthracenedione-based regimen (unless contraindicated) • Third-line and later in patients with DLBCL after ≥2 prior chemoimmunotherapy regimens
Investigational T-Cell Therapy Targeting EBV	Settings Under Late-Stage Investigation
Tabelecleucel	Phase III ALLELE trial investigating EBV-positive posttransplant lymphoproliferative disorder in settings of⁸: • Solid organ transplant after failure of rituximab and rituximab plus chemotherapy • Allogeneic stem cell transplant after rituximab failure

ALL, acute lymphoblastic lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; NCCN, National Comprehensive Cancer Network; NOS, not otherwise specified; R/R, relapsed/refractory.

Dosage and Administration Considerations^{2-5,9-12}

- All approved CAR T-cell therapies must be administered at certified healthcare facilities per the Risk Evaluation and Mitigation Strategy (REMS)
 - Patients must remain either inpatient or outpatient close to the certified healthcare facility for at least 4 weeks after infusion to be monitored for acute adverse events

- The manufacturing process for autologous CAR T-cells requires a median duration of 24-113 days from leukapheresis to infusion of CAR T-cells
 - Bridging therapy may be needed to control disease in some patients during the wait
- Before receiving FDA-approved CD19-directed CAR T-cells, patients must receive a lymphodepleting chemotherapy regimen of cyclophosphamide plus fludarabine

FDA-Approved CAR T-Cell Therapy		Dosing in Lymphomas
Axicabtagene ciloleucel	• Lymphodepleting regimen: cyclophosphamide 500 mg/m² IV plus fludarabine 30 mg/m² IV on the fifth, fourth, and third days before CAR T-cell infusion • CAR T-cell target dose: single infusion of 2×10^6 CAR-positive viable T-cells/kg (maximum: 2×10^8)	
Brexucabtagene autoleucel	• Lymphodepleting regimen: cyclophosphamide 500 mg/m² IV plus fludarabine 30 mg/m² IV on the fifth, fourth, and third days before CAR T-cell infusion for MCL or fludarabine 25 mg/m² IV on the fourth, third, and second days and cyclophosphamide 900 mg/m² IV on the second day before CAR T-cell infusion for ALL • CAR T-cell target dose: single infusion of 2×10^6 CAR-positive viable T-cells/kg (maximum: 2×10^8) for MCL or 1×10^6 CAR-positive viable T-cells/kg (maximum: 1×10^8) for ALL	
Lisocabtagene maraleucel	• Lymphodepleting regimen: cyclophosphamide 300 mg/m² IV plus fludarabine 30 mg/m² IV for 3 days, with CAR T-cell infusion 2-7 days after completing lymphodepleting chemotherapy • CAR T-cell target dose: single infusion of $50\text{-}110 \times 10^6$ CAR-positive viable T-cells	
Tisagenlecleucel	• Lymphodepleting regimen for DLBCL: – Cyclophosphamide 250 mg/m² IV plus fludarabine 25 mg/m² IV for 3 days starting with first fludarabine dose (<i>alternative if patient experienced prior grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to prior cyclophosphamide-containing regimen:</i> bendamustine 90 mg/m² IV daily for 2 days) – Infuse CAR T-cells 2-11 days after completing lymphodepleting chemotherapy • Lymphodepleting regimen for pediatric/young adult B-cell ALL: – Cyclophosphamide 500 mg/m² IV for 2 days plus fludarabine 30 mg/m² IV for 4 days starting with first fludarabine dose – Infuse CAR T-cells 2-14 days after completing lymphodepleting chemotherapy • CAR T-cell target dose: single infusion of $0.6\text{-}6.0 \times 10^8$ CAR-positive viable T-cells for adults with DLBCL or $0.2\text{-}5.0 \times 10^6$ CAR-positive viable T-cells/kg for pediatric/young adult B-cell ALL for patients ≤ 50 kg or $0.1\text{-}2.5 \times 10^8$ CAR-positive viable T-cells for pediatric/young adult B-cell ALL for patients > 50 kg	
Investigational T-Cell Therapy		
Tabelecleucel	In the phase III ALLELE trial^{13,14}: • Tabelecleucel infused at dose of 2×10^6 cells/kg on Days 1, 8, 15 of 35-day cycles • Response assessed at end of each cycle • Treatment continued until maximal response, unacceptable toxicity, use of nonprotocol therapy, or response failure to tabelecleucel with ≤ 2 different HLA restrictions*	

*Tabelecleucel partially matched to each patient from library of HLA-characterized tabelecleucel based on 1 EBV HLA restriction allele plus ≥ 1 other matched HLA allele.

Acute Adverse Event Management

- Key adverse events with T-cell therapy: cytokine-release syndrome (CRS) and neurotoxicity/immune effector cell-associated neurotoxicity syndrome (ICANS)^{15,16}
 - CRS: potentially life-threatening toxicity caused by immune activation of T-cells, resulting in elevated inflammatory cytokines and activation of other immune cells; key symptoms include fever, hypotension, hypoxia
 - ICANS: likely related to T-cell activation; key symptoms include diminished attention, language disturbance, confusion, disorientation, agitation, aphasia, tremors, seizures, encephalopathy

- Both CRS and ICANS should be graded per the 2019 American Society for Transplantation and Cellular Therapy (ASTCT) guidelines¹⁶
 - CRS grading depends on the severity of fever, hypotension, and hypoxia
 - ICANS grading depends on immune effector cell-associated encephalopathy (ICE) score, level of consciousness, seizure, motor findings, and elevated intracranial pressure/cerebral edema

Grade per ASTCT 2019 Guidelines ^{16,17}	CRS	ICANS	CRS + ICANS
1	- Supportive care - Consider tocilizumab and/or steroids (dexamethasone)	Supportive care	- Supportive care - Tocilizumab
2	- Supportive care - Tocilizumab - Consider steroids (dexamethasone)	- Supportive care - Steroids (dexamethasone)	- Supportive care - Tocilizumab - Steroids (dexamethasone)
3	- ICU care - Tocilizumab + steroids (dexamethasone)	- ICU care - Steroids (dexamethasone or methylprednisolone)	- ICU care - Tocilizumab - Steroids (dexamethasone or methylprednisolone)
4	- ICU care - Tocilizumab + steroids (dexamethasone or methylprednisolone)	- ICU care - High-dose steroids (dexamethasone or methylprednisolone)	- ICU care - Tocilizumab - High-dose steroids (dexamethasone or methylprednisolone)

Additional Adverse Events Associated With CAR T-Cell Therapy

- Additional shorter-term adverse events can include hemophagocytic lymphohistiocytosis/macrophage activation syndrome and immunosuppression
- Longer-term events to monitor for include B-cell aplasia, cytopenias, and infections; consult institutional guidelines for management of the following toxicities and contact CAR T-cell treatment center for special management questions²⁻⁵
 - B-cell aplasia/hypogammaglobulinemia
 - Occurred in up to ~30% of adults with R/R large B-cell lymphoma or MCL treated with approved agents
 - Immunoglobulin levels should be monitored following therapy
 - Cytopenias
 - Grade ≥ 3 cytopenias unresolved by Day 30 post treatment occur in a significant proportion of patients
 - Blood counts should be monitored following therapy
 - Infections
 - Occurred in 38% to 70% of patients treated with approved agents in pivotal trials

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