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Tisagenlecleucel

A clinical overview of KYMRIA[®]

Tisagenlecleucel is a CD19-directed genetically modified autologous CAR T-cell therapy incorporating a CD8 hinge/transmembrane region, 4-1BB costimulatory domain, and CD3 ζ signaling domain.



Indications



Treatment Overview & Dose



Lymphodepleting Chemotherapy



Infusion & Monitoring



Cytokine Release Syndrome

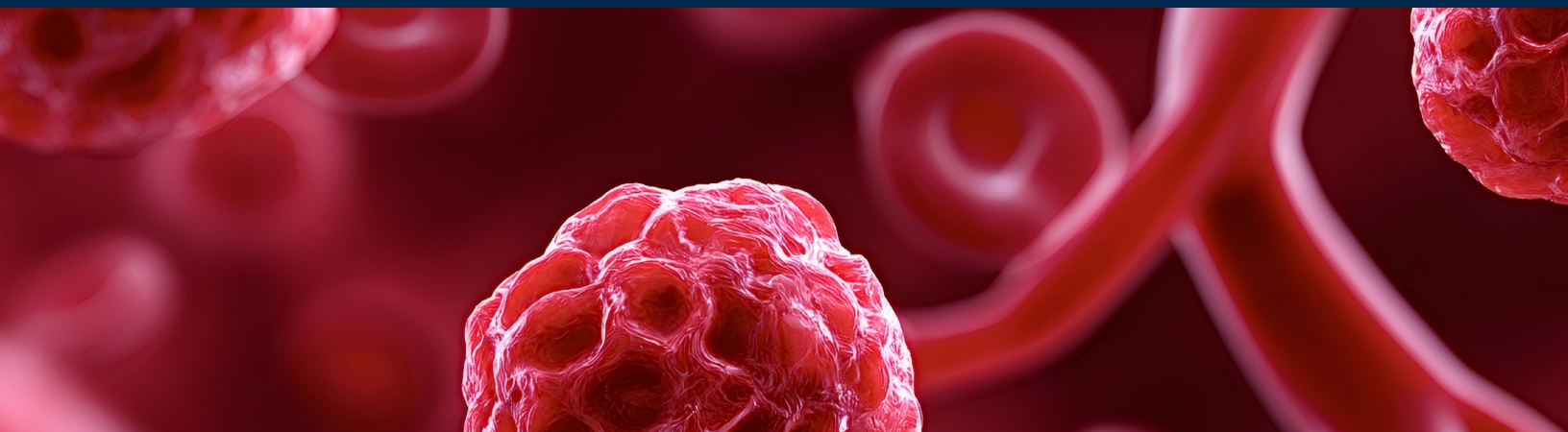


Neurologic Toxicities



Other Clinically Significant Risks

This resource is an educational summary and does not replace the full prescribing information, institutional CAR T-cell protocols, or patient-specific clinical judgment.



Tisagenlecleucel is indicated for the treatment of:

B-cell precursor acute lymphoblastic leukemia

Treatment of B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse in patients up to 25 years of age.

Large B-cell lymphoma (LBCL)

Treatment of relapsed or refractory large B-cell lymphoma in adults (after 2 or more lines of systemic therapy), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Follicular lymphoma (FL)

Treatment of relapsed or refractory (r/r) follicular lymphoma in adults (after 2 or more lines of systemic therapy).

IMPORTANT LIMITATIONS

For the LBCL indication, tisagenlecleucel is not indicated for primary CNS lymphoma. The follicular lymphoma indication is under accelerated approval.

Product-specific requirements

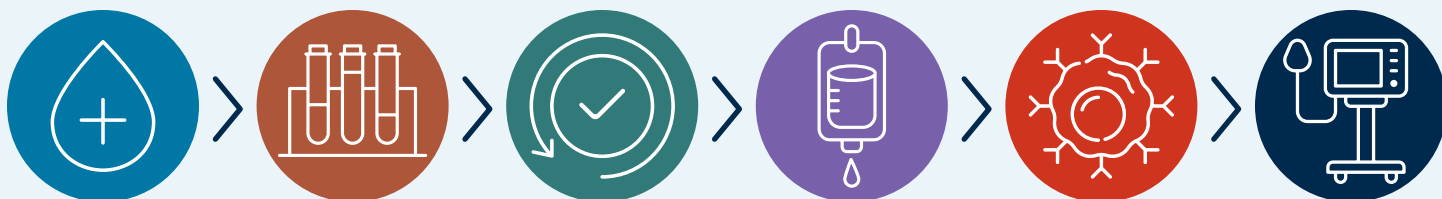
For autologous and intravenous use only.

Confirm that the patient identity matches the identifiers on every patient-specific infusion bag. Do not infuse if the information does not match.

Do not administer tisagenlecleucel to patients with active infection or inflammatory disorders.



Treatment Overview & Dose



Step	Clinical action
1. Leukapheresis	Collect the patient's peripheral blood mononuclear cells for manufacturing.
2. Manufacturing period	Tisagenlecleucel is manufactured as a patient-specific autologous T-cell product in 1–3 infusion bags. Manufacturing generally takes about 3–4 weeks from receipt of cells at the manufacturing site to shipment back to the health care provider; timing may vary.
3. Confirm product availability	Confirm that tisagenlecleucel is available before beginning lymphodepleting chemotherapy.
4. Lymphodepletion	Use the indication-specific regimen if lymphodepletion is needed.
5. Tisagenlecleucel infusion	Administer all patient-specific bags as a single treatment dose within the indication-specific window.
6. Early monitoring	Monitor daily during the first week and continue monitoring for at least 2 weeks after infusion.

Recommended tisagenlecleucel dose

Population	Dose
B-cell ALL; ≤50 kg	$0.2\text{--}5.0 \times 10^6$ CAR-positive viable T cells/kg
B-cell ALL; >50 kg	$0.1\text{--}2.5 \times 10^8$ CAR-positive viable T cells
Adult LBCL or FL	$0.6\text{--}6.0 \times 10^8$ CAR-positive viable T cells

Before infusion

Confirm that at least 2 doses of tocilizumab and emergency equipment are available before infusion and during recovery.

Do not use a leukodepleting filter.

Verify the patient's identity immediately before administration.

Delay infusion for unresolved serious adverse reactions from preceding chemotherapy (including pulmonary or cardiac reactions or hypotension), active uncontrolled infection, active graft-versus-host disease, or worsening leukemia burden after lymphodepletion.

Lymphodepleting Chemotherapy



Confirm product availability before lymphodepletion. The regimen and infusion interval depend on the indication.

B-cell ALL regimen

Agent	Dose and schedule	Infusion interval
Fludarabine	30 mg/m ² IV daily for 4 days	2–14 days after completion
Cyclophosphamide	500 mg/m ² IV daily for 2 days, starting with the first fludarabine dose	—

Adult LBCL and FL regimen

Agent	Dose and schedule	Infusion interval
Fludarabine	25 mg/m ² IV daily for 3 days	LBCL: 2–11 days; FL: 2–6 days
Cyclophosphamide	250 mg/m ² IV daily for 3 days, starting with the first fludarabine dose	—

ALTERNATIVE OR OMISSION

For LBCL/FL, bendamustine 90 mg/m² IV daily for 2 days may be used after prior Grade 4 cyclophosphamide-associated hemorrhagic cystitis or cyclophosphamide resistance. Lymphodepletion may be omitted for significant cytopenia (eg, WBC count $<1 \times 10^9/\text{L}$ within 1 week before infusion).

Premedication before tisagenlecleucel

Premedicate 30–60 minutes before infusion with acetaminophen and diphenhydramine or another H1-antihistamine.

Avoid prophylactic systemic corticosteroids because they may interfere with the activity of tisagenlecleucel.

Live-virus vaccines

Live-virus vaccination is not recommended for at least 6 weeks before lymphodepleting chemotherapy, during tisagenlecleucel treatment, and until immune recovery.



Infusion & Monitoring



Administration

- 1. Inspect and thaw:** Inspect the bag for damage or leaks and place inside a second sterile bag. Thaw at 37°C until no ice remains. If multiple bags are required, thaw and administer 1 bag at a time.
- 2. Prepare product:** Gently mix to disperse cell clumps. Do not infuse if clumps persist or the bag is compromised. Do not wash, centrifuge, or resuspend in new media. Infuse within 30 minutes once thawed and at room temperature.
- 3. Prepare infusion:** Prime tubing with NS. Do not use a leukocyte-depleting filter.
Infuse: Administer the entire bag (10–50 mL) IV at 10–20 mL/minute; adjust the rate for smaller volumes.
Rinse: Maintaining a closed system, rinse the bag with 10–30 mL NS to ensure maximum cell delivery.
- 4. Additional bags:** Confirm each bag was safely administered before thawing the next. Administer all bags to complete the dose.

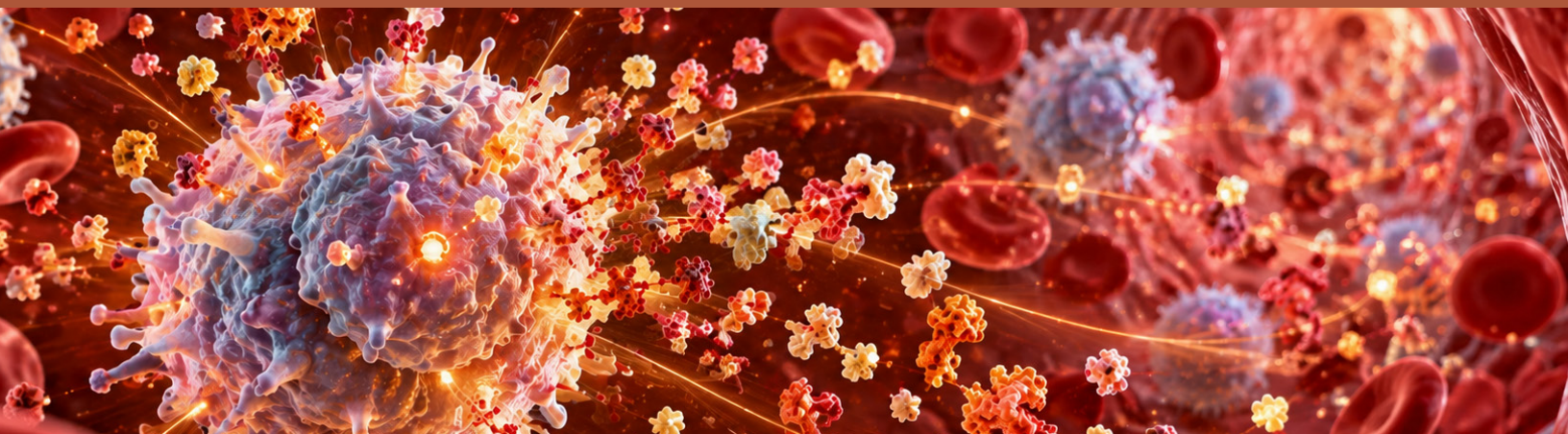
Required monitoring

Period	Recommendation
First week	Monitor daily for signs and symptoms of cytokine release syndrome (CRS) and neurologic toxicities.
At least 2 weeks	Continue monitoring and instruct the patient to remain near a healthcare facility. Avoid driving or operating heavy or potentially dangerous machinery.
Long term	Monitor blood counts, immunoglobulin levels, and infection risk as clinically indicated. Monitor lifelong for secondary malignancies.

PATIENT EDUCATION

Patients and caregivers should understand that CRS and neurologic symptoms require immediate medical evaluation—even when they occur after the initial monitoring period. Advise patients not to donate blood, organs, tissues, sperm, oocytes, or other cells.

Cytokine Release Syndrome



CRS is a systemic inflammatory response that may be fatal or life-threatening. It can present with fever, hypotension, tachycardia, chills, hypoxia, headache, fatigue, and organ dysfunction.

Population	Trial Name	Any-grade CRS	Grade 3 or higher	Median onset	Median resolution
B-cell ALL	ELIANA	77%	48%	3 days	8 days
DLBCL	JULIET	74%	23%	3 days	7 days
FL	ELARA	53%	0%	4 days	4 days

Why it matters

- CRS may occur concurrently with neurologic toxicity and may be associated with arrhythmias, renal insufficiency, cardiac or respiratory failure, capillary leak syndrome, multiorgan failure, and HLH (hemophagocytic lymphohistiocytosis)/MAS (macrophage activation syndrome).
- Safety populations: B-cell ALL, N=79; DLBCL, N=115; FL, N=97. CRS was graded using the Penn system for B-cell ALL and DLBCL and the Lee system for FL.
- In B-cell ALL, risk factors for severe CRS include >50% bone marrow blasts before infusion, uncontrolled or accelerating tumor burden after lymphodepletion, and active infection or inflammatory processes.
- Ensure that at least 2 doses of tocilizumab and emergency equipment are available before infusion.
- At the first sign of CRS, immediately evaluate for hospitalization and alternative causes of fever, hypoxia, and hypotension. Initiate supportive care, tocilizumab, and/or corticosteroids as indicated by severity and current management guidance.

THE BOTTOM LINE

CRS is common and may be fatal or life-threatening. Risk and severity vary by indication, with the highest Grade 3 or higher rate in B-cell ALL. Early evaluation and protocol-directed treatment are essential.



Neurologic Toxicities

(including ICANS)



Neurologic toxicities may be fatal or life-threatening and may occur concurrently with CRS, after CRS resolves, or in the absence of CRS.

Population	Trial Name	Any-grade neurologic toxicity	Grade 3 or higher	Median onset	Median duration
B-cell ALL	ELIANA	71%	22%	6 days	7 days
DLBCL	JULIET	60%	19%	5 days	17 days
FL	ELARA	43%	6%	8 days	5 days

Common manifestations

- Headache, encephalopathy, delirium, anxiety, sleep disorders, dizziness, tremor, peripheral neuropathy, seizures, and aphasia.
- Events may occur concurrently with CRS, after CRS resolves, or in the absence of CRS.

Management principles

- Monitor daily during the first week and continue monitoring for at least 2 weeks after infusion.
- Promptly evaluate new neurologic symptoms and provide supportive care and/or corticosteroids according to severity and current management guidance.
- Consider non-sedating seizure prophylaxis (eg, levetiracetam) in patients at higher risk for seizure, such as those with a seizure history, central nervous system (CNS) disease, concerning electroencephalogram (EEG) findings, or neoplastic brain lesions.
- Advise patients to avoid driving for at least 2 weeks after infusion.

THE BOTTOM LINE

Neurologic toxicity is common and may be prolonged, severe, or fatal. Symptoms can occur after CRS has resolved, so continued monitoring and rapid evaluation are critical.



Other Clinically Significant Risks



Serious infections

- Infections occurred in 72% of patients with B-cell ALL, 58% with DLBCL, and 52% with FL; Grade 3 or higher rates were 48%, 33%, and 21%, respectively.
- Screen for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) before cell collection and manage according to clinical guidelines.
- Monitor for infection before and after infusion and administer prophylactic antimicrobials according to local guidelines.
- Febrile neutropenia may occur concurrently with cytokine release syndrome (CRS). Opportunistic fatal central nervous system (CNS) infections, including progressive multifocal leukoencephalopathy (PML) due to John Cunningham (JC) virus reactivation, have occurred after tisagenlecleucel; perform appropriate diagnostic evaluation for new neurologic adverse events. Hepatitis B virus (HBV) reactivation may also occur. Some commercial human immunodeficiency virus (HIV) nucleic acid tests may yield false-positive results after tisagenlecleucel.

Prolonged cytopenias

- At Day 28, unresolved Grade 3 or higher neutropenia/thrombocytopenia occurred in 40%/27% of ALL responders, 25%/39% of DLBCL patients, and 16%/17% of FL patients.
- Monitor complete blood counts after infusion. Myeloid growth factors, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF), are not recommended during the first 3 weeks after infusion or until CRS has resolved.

Hypogammaglobulinemia

- Hypogammaglobulinemia and agammaglobulinemia related to B-cell aplasia may occur after tisagenlecleucel. Hypogammaglobulinemia occurred in 53% of patients with B-cell ALL, 17% with DLBCL, and 18% with FL.
- Monitor immunoglobulin levels and manage with infection precautions, antibiotic prophylaxis, and immunoglobulin replacement as clinically indicated.

Additional Warnings & Populations

HLH/MAS

HLH/MAS occurred in 6% of patients with B-cell ALL and 2% with DLBCL; these events occurred with ongoing CRS and resolved. One patient with FL developed fatal HLH more than 1 year after infusion without concurrent CRS.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, may be related to dimethyl sulfoxide or dextran 40. Monitor during and after infusion and treat promptly.

Secondary malignancies

Secondary malignancies—including mature T-cell malignancies and CAR-positive tumors—have occurred after genetically modified autologous T-cell immunotherapies and may be fatal.

- Monitor lifelong for secondary malignancies.
- If a secondary malignancy occurs, contact Novartis Pharmaceuticals Corporation at 1-844-459-6742 for sample-collection instructions.

Use in specific populations

Population	PI guidance
Pregnancy	Tisagenlecleucel is not recommended during pregnancy. Verify pregnancy status before treatment and assess immunoglobulin levels in exposed newborns.
Contraception	Refer to the fludarabine and cyclophosphamide PIs. Data are insufficient to recommend a contraception duration after tisagenlecleucel.
Lactation	No data are available. Consider the benefits of breastfeeding, the clinical need for tisagenlecleucel, and potential risks to the infant.
Pediatric use	Safety and efficacy are established for B-cell ALL in patients up to age 25; they are not established for pediatric LBCL or FL.
Geriatric use	Safety and efficacy are not established in geriatric patients with B-cell ALL. Studies included insufficient patients ≥ 65 years to determine whether responses differ.

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