GENE AND CELLULAR THERAPY - CAR-T Cell Immunotherapy

Tisagenlecleucel (Tisa-cel, Kymriah; Novartis Pharmaceuticals Corporation**)**
FDA Approval Date: 5/1/2018

AHFS PHARMACOLOGIC THERAPEUTIC CLASS
26:12 - Gene Therapy; 10:00 - Antineoplastic Agents
LEXI-COMP PHARMACOLOGIC THERAPEUTIC CLASS
Antineoplastic Agent, Anti-CD19; Antineoplastic Agent, CAR-T Immunotherapy; CAR-T Cell Immunotherapy; Cellular Immunotherapy, Autologous; Chimeric Antigen Receptor T-Cell Immunotherapy
NCCN CATEGORY
Category 2A

CURRENT FORMULARY STATUS WITHIN ENTERPRISE
Formulary

COMPARATIVE AGENTS
DLBCL - Axicabtagene ciloleucel (Yescarta) and lisocabtagene maralecuel (Breyanzi)

AVAILABLE FORMULATIONS[1]
Suspension for intravenous infusion [contains albumin human, dextran 40, dimethyl sulfoxide]

INDICATIONS[1]
FDA Approved
- 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.
- 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.
    - Limitation of use: not indicated for treatment of primary CNS lymphoma.

Off-Label uses
- None

DESCRIPTION AND CLINICAL PHARMACOLOGY[1,2]
Tisa-cel is a CD19-directed, genetically modified, autologous T cell immunotherapy in which a patient's T-cells are harvested through leukapheresis and reprogrammed with a transgene encoding a chimeric antigen receptor (CAR). CAR consists of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from CD3 zeta and 4-1BB (CD137). CD3-zeta signaling initiates activation and antitumor activity, while 4-1BB (CD137) enhances T-cell expansion. After identifying and binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the tisa-cel cells.

PHARMACODYNAMICS AND PHARMACOKINETICS[123]

Distribution	High distribution into bone marrow.
Duration	Due to the mechanism of action, a period of B-cell aplasia is expected. ALL: 33% of patients had no detectable B cells at baseline; at month 24, 88% had no detectable B cells. DLBCL: majority of patients had B cell depletion at baseline; at month 24, no patients had detectable B cells.
Half-life, elimination	ALL: ~17 days (in responding patients). DLBCL: ~45 days (in responding patients).
Time to Peak	~10 days (in responding patients).
Expansion	Tisa-cel exhibits an initial rapid expansion followed by a bi-exponential decline; it is present in blood and bone marrow and is measurable beyond 2 years in patients with ALL and up to 18 months (in peripheral blood) and up to months (in marrow) in patients with DLBCL. In patients who received tocilizumab to manage cytokine release syndrome, tisa-cel's AUC and Cmax are 238% and 311% higher in patients with DLBCL, and 298% and 183% higher in patients with ALL. In patients who received corticosteroids for CRS, tisa-cel's AUC and Cmax are 114% and 179% higher in patients with DLBCL and the AUC was 280% higher in patients with ALL.

DOSING AND ADMINISTRATION[12]

- For autologous IV use only. Confirm patient identity matches cassette and infusion bag prior to infusion. A single dose may be contained in 1 to 3 patient-specific infusion bags.
- Premedication - Premedicate with acetaminophen and diphenhydramine (or another H1-antihistamine) ~30-60 minutes prior to tisa-cel infusion. Avoid prophylactic use of corticosteroids as they may interfere with tisa-cel activity. Begin infection prophylaxis (according to local recommendations) prior to initiating tisa-cel.
- Delay tisa-cel for unresolved serious adverse reactions from chemotherapy or active uncontrolled infection, active graft vs host disease (GVHD), or worsening leukemia burden following lymphodepleting chemotherapy.
- Ensure that tocilizumab is available (minimum of 2 doses) on site prior to tisa-cel infusion.
- Administer at a REMS-certified healthcare facility.

Indication	Dosing
ALL: IV	● A treatment course of lymphodepleting chemotherapy (with fludarabine and cyclophosphamide) followed by tisa-cel 2 to 14 days following completion. ● Dosing is based on weight reported at the time of leukapheresis: ○ **<25 years and ≤50 kg: IV 0.2 to 5 x 10^6 CAR^+ viable T cells** ○ **<25 years and >50 kg: IV 0.1 to 2.5 x 10^8 CAR^+ viable T cells**
DLBCL: IV	● A treatment course of lymphodepleting chemotherapy (with fludarabine and cyclophosphamide or with bendamustine for cyclophosphamide intolerance or resistance) followed by tisa-cel 2 to 11 days following completion. ○ Lymphodepleting chemotherapy may be omitted if the WBC ≤1,000/mm^3 within 1 week prior to tisa-cel infusion. ● **Target dose: 0.6 to 6 x 10^8 CAR^+ viable T cells.**

Geriatric
- Refer to DLBCL dosing.

Pediatric
- Refer to ALL dosing.

Renal impairment
- Has not been studied - there are no dosage adjustments provided in the manufacturer's labeling.

Hepatic impairment
- Has not been studied - there are no dosage adjustments provided in the manufacturer's labeling.

LITERATURE REVIEW AND CLINICAL EFFICACY[45]

In a phase 2 clinical study, Tisa-cel produced high remission rates and durable remissions without additional therapy in high-risk pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects. Tisa-cel reported an overall remission rate of 81%, complete remission rate of 60%, 6-month relapse-free survival (RFS) rate of 80%, 12-month RFS rate of 59%, 6-month rate of event-free survival of 73%, 12-month rate of event-free survival of 50%, 6-month rate of overall survival (OS) of 90%, and 12-month rate of OS of 76%.

In the phase 2 JULIET clinical study, tisa-cel demonstrated high and durable response rates in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), though follow-up was short and there is a potential for long-term toxic effects that requires further analysis. Tisa-cel reported an overall response rate (ORR) of 52%, complete response (CR) rate of 40%, durable responses seen up to 18.4 months, 12-month estimated progression-free survival (PFS) of 83%, median overall survival (OS) of 12 months with 12-month estimated probability of survival of 49% in all patients and 90% in those with CR.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS[12]

Black Box Warnings
- Cytokine Release Syndrome (CRS)
  - Grade 3 and higher CRS reactions have occurred.
  - Median time to onset: 3 days, median duration: 7 or 8 days
  - ALL - Tocilizumab use: 50%, some patients required addition of corticosteroids
  - DLBCL - Tocilizumab use: 20%, some used corticosteroids
- Neurological Toxicities
  - Grade 3 and higher neurotoxicity's have occurred.
  - Median time to first event 5 to 6 days, most occurred within 8 weeks following infusion
  - ALL median duration: 7 days, DLBCL median duration: 17 days
  - Neurotoxicity generally resolved within 21 days, encephalopathy reported up to 50 days
- REMS program

Contraindications

There are no contraindications listed in the manufacturer's labeling.

Warnings and Precautions
- Cytopenia's
  - Prolonged cytopenia's may occur several weeks after lymphodepleting chemotherapy and tisa-cel infusion. Unresolved (by day 28) grade 3 or higher cytopenia's included neutropenia and thrombocytopenia. Some patients still experienced grade 3 or higher neutropenia or thrombocytopenia at 56 days post infusion. Prolonged neutropenia is associated with an increased risk of infection.
- Hepatitis B virus reactivation

    - HBV reactivation (sometimes resulting in fulminant hepatitis, hepatic failure and death) can occur in patients treated with medications directed against B cells.
- Hypersensitivity
    - Allergic reactions may occur with tisa-cel infusion. Serious hypersensitivity reactions, including anaphylaxis, may occur due to the dimethyl sulfoxide (DMSO) or dextran 40 components in tisa-cel.
- Hypogammaglobulinemia and IgG agammaglobulinemia related to B-cell aplasia
- Infection
    - Infections (including life-threatening or fatal infections occurred in patients after tisa-cel infusion, including grades 3 and higher infections. Neutropenic fever (grade 3 or higher) has been observed after tisa-cel infusion and may occur concurrently with CRS. There is no experience manufacturing tisa-cel for patients with a positive HIV test or with active HBV or hepatitis C virus.
- Secondary malignancies

ADVERSE REACTIONS[3]

Common

- Cardiovascular: Hypotension (26% to 31%), Tachycardia (13% to 26%)
- Gastrointestinal: Decrease in appetite, Relapsed or refractory diffuse large B-cell lymphoma (12%), B-cell precursor acute lymphoblastic leukemia (37%), Diarrhea (26% to 31%), Nausea (26% to 27%), Vomiting (26%)
- Immunologic: Infectious disease, Unspecified pathogen (41% to 42%)
- Neurologic: Encephalopathy (16% to 34%), Headache (21% to 37%)
- Other: Fever (34% to 40%)

Serious

- See “Contraindications, Warnings, and Precautions” above.
- Other
    - Immunologic: Relapsed or refractory diffuse large B-cell lymphoma (14%); B-cell precursor acute lymphoblastic leukemia, (43%), Mycosis (13%)

Dose Adjustments for Toxicity[1]

Cytokine Release Syndrome

- Evaluate patients immediately at the first sign of CRS. Myeloid growth factors, particularly GM-CSF (sargramostim), are not recommended during the first 3 weeks after tisa-cel infusion or until CRS has resolved.

CRS Severity	Recommendation
Prodromal syndrome (low-grade fever, fatigue, anorexia)	Observe the patient, exclude infection, administer antibiotics (per local guidelines) if neutropenic, manage symptomatically.
CRS requiring mild intervention (one or more of the following: high fever, hypoxia, and/or mild hypotension)	Administer antipyretics, oxygen, IV fluids, and/or low-dose vasopressors as needed.
CRS requiring moderate to aggressive intervention (one or more of the following: hemodynamic instability despite IV fluids and vasopressor support, worsening respiratory distress, rapid clinical	Administer high-dose or multiple vasopressors, oxygen, mechanical ventilation and/or other supportive care as needed. Administer IV tocilizumab over 1 h (patients ≥30 kg: 8 mg/kg). If no clinical improvement, repeat tocilizumab as needed within at least an 8 h interval between consecutive doses; if no response, consider a third

deterioration)	dose or pursue alternative CRS management. If no clinical improvement within 12 to 18 h of the first dose or worsening at any time, administer methylprednisolone 2 mg/kg initially, then 2 mg/kg/day until vasopressors and high-flow oxygen are no longer needed, then taper corticosteroids.

*Do not exceed 3 tocilizumab doses in 24 hours and a maximum total of 4 tocilizumab doses.

Other Toxicities

Toxicity	Recommendation
Hypogammaglobulinemia	Manage with IV immune globulin replacement and with infection precautions and antibiotic and/or antiviral prophylaxis as indicated.
Neurologic toxicity	Exclude other causes and manage with supportive care as clinically indicated.
Neutropenic fever	Evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as clinically indicated.

RISK EVALUATION AND MITIGATION STRATEGIES[6]

KYMRIAH REMS

- Hospitals and their associated clinics that dispense tisa-cel must be specially certified and have on-site, immediate access to tocilizumab.
- Those who prescribe, dispense, or administer tisa-cel must be aware of how to manage the risks of cytokine release syndrome and neurological toxicities.
- Kymriah is only available at select treatment centers.
- Further information is available at https://www.kymriah-rems.com/ or contact Novartis at 1-844-4KYMRIAH.

MAJOR INTERACTIONS[1]

Drug-Drug (Risk X - Avoid Combination)

- Immunizations
    - Live Vaccines - immunosuppressants may enhance the adverse/toxic effect of live vaccines. Immunosuppressants may diminish the therapeutic effect of live vaccines. Avoid use of live organism vaccines with immunosuppressants, live-attenuated vaccines should not be given for at least 3 months after immunosuppressants.
    - Measles, Mumps, and Rubella Virus Vaccine - immunosuppressants may enhance the adverse/toxic effects of MMR Virus Vaccine.
    - Varicella Virus Vaccine - immunosuppressants may enhance the adverse/toxic effect of Varicella Virus Vaccine.
- BCG (Intravesical) - immunosuppressants may diminish the therapeutic effect of BCG.
- Cladribine - may enhance the immunosuppressive effect of immunosuppressants.
- Granulocyte Colony-Stimulating Factors - may enhance the adverse/toxic effect of tisa-cel.
- Natalizumab - immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased.
- Pimecrolimus - may enhance the adverse/toxic effects of immunosuppressants.
- Tacrolimus (topical) - may enhance the adver/se toxic effects of immunosuppressants.
- Talimogene Laherparepvec - immunosuppressants may enhance the adverse/toxic effects of talimogene laherparepvec. Specifically, the risk for disseminated herpetic infection may increase.
- Upadacitinib - immunosuppressants may enhance the immunosuppressive effect of upadacitinib.

Drug-Disease

- HIV and the lentivirus used to make tisa-cel have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests may yield false-positive results in patients who have received tisa-cel.

MONITORING REQUIREMENTS[1,2]

- Screen for HBV, HCV, and HIV prior to collection of cells for manufacturing.
- Evaluate pregnancy status prior to use.
- Monitor immunoglobulin levels (IgG) after treatment.
- Monitor for signs/symptoms of CRS and neurotoxicity 2 to 3 times during the first week following infusion; monitor for signs/symptoms of CRS for at least 4 weeks after treatment.
- Monitor for signs/symptoms of hypersensitivity, infection, and secondary malignancies.

PREGNANCY/BREASTFEEDING[1]

- Evaluate pregnancy status prior to use in patients who may become pregnant. The duration of contraception needed following tisa-cel administration is not known.
- Based on MOA, if placental transfer were to occur, fetal toxicity, including B-cell lymphocytopenia may occur.
- Pregnant patients who have received tisa-cel may have hypogammaglobulinemia.
    - Assess immunoglobulin levels in newborns of mothers treated with tisa-cel.
- It is not known if tisa-cel is present in breast milk.

MEDICATION SAFETY ISSUES[1]

Sound/Look Alike issues

- Kymriah may be confused with Kynamro.
- Tisagenlecleucel may be confused with axicabtagene ciloleucel, brexucabtagene autoleucel, idecabtagene vicleucel, lisocabtagene maraleucel, sipulecel-T.

High Alert Medication

- This medication is in a class the Institute for Safe Medication Practices (ISMP) lists of drug classes which have heightened risk for causing significant patient harm when used in error.

SPECIAL STORAGE PRECAUTIONS[1]

- Store infusion bag(s) in a temperature-monitored system ≤ -120°C (e.g., in the vapor phase of liquid nitrogen).
- After thawing, it may only be stored for up to 30 minutes at room temperature of 20 to 25°C.

SPECIAL HANDLING/ADMINISTRATION[1,2]

- Tisa-cel contains human blood cells that are genetically modified with replication-incompetent, self-inactivating lentiviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid transmission of infectious diseases.
- Before thawing, inspect the infusion bag(s) for breaches of container integrity (i.e. breaks or cracks); contact the manufacturer if compromised. If >1 bag is received, thaw 1 bag at a time and do not initiate thawing of the next bag until infusion of the previous bag is complete.
- To thaw, place the bag inside a second sterile bag and thaw at ~37℃ using an appropriate thaw device or water bath) until there is no visible ice in the infusion bag.
- Gently mix the bag contents to disperse cellular material clumps. If visible clumps remain, continue to gently mix the contents.
- Do not wash, spin down, and/or resuspend in new media prior to infusion.

- Prime tubing set with NS prior to infusion. Infuse tisa-cel at a rate of 10 to 20 mL/minute, infuse entire contents of the bag, then rinse the infusion bag with 10 to 30 mL NS to assure as many cells as possible are infused.
- Do not use a leukodepletion filter. A central line may be used for administration.

COST AND REIMBURSEMENT INFORMATION[7]

Cost (Estimated WAC)	$475,000
Medical/Pharmacy Benefit	Medical
Inpatient/Outpatient	Outpatient
HCPCS Code	Q0242 tisagenlecleucel (600 million cells) - Tisagenlecleucel, up to 600 million CAR + viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose.
NOC Code Billing Guide	SEE IPD CODESOURxCE

PATIENT ASSISTANCE AVAILABILITY[8]

- KYMRIAH CARES™ is a support program designed to provide patients with support programs to help access Kymriah therapy.
- Provides access to resources for patients who are receiving KYMRIAH, patient support programs, information about insurance coverage, and more.
- Additional information available at 1-844-459-6742 from 8:00 AM to 8:00 PM ET.

REFERENCES

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