GENE AND CELLULAR THERAPY - CAR-T Cell Immunotherapy

Axicabtagene Ciloleucel (Axi-cel, Yescarta; Kite Pharma, Inc**)**
Original FDA Approval Date: DLBCL- 10/18/2017; Follicular Lymphoma 3/05/2021

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 - Tisagenlecluecel (Kymriah) and lisocabtagene maralecuel (Breyanzi)
FL - none

AVAILABLE FORMULATIONS[1]
Suspension for intravenous infusion (preservative free) [contains DMSO and albumin human]

INDICATIONS[12]
FDA Approved
- Treatment of relapsed or refractory follicular lymphoma in adults after ≥2 lines of systemic therapy.
- Treatment of relapsed or refractory large B-cell lymphoma in adults after ≥2 lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
    - Limitations of use: not indicated for the treatment of patients with primary CNS lymphoma.

Off-Label uses
- None

DESCRIPTION AND CLINICAL PHARMACOLOGY[12]
Axi-cel is a CD19-directed, genetically modified, autologous T-cell immunotherapy in which patients T cells are harvested through leukapheresis, then reprogrammed with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal cells. The CAR consists of a murine single-chain antibody fragment which recognizes CD19 and is fused to CD28 and CD3 zeta. CD3 zeta is a critical component for initiating T-cell activation and antitumor activity. After binding to CD19-expressing cells, the CD28 and CD3 zeta costimulatory domains activate downstream signaling cascades resulting in T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. The sequence of these events leads to the killing of CD19-expressing cells.

PHARMACODYNAMICS AND PHARMACOKINETICS[12]

Onset	Median time to response: 1 month
Duration	Anti-CD19 CAR T cells displayed an initial rapid expansion followed by a decline to near baseline levels by 3 months post infusion.
Time to Peak	Peak levels occurred within the first 7-14 days after infusion.
Other	The number of anti-CD19 CAR T cells in the blood was positively correlated with objective response. The median anti-CD19 CAR T cell C_{max} levels in patients with refractory DLBCL who responded to therapy were 205% higher compared with the levels in non-responding patients.

DOSING AND ADMINISTRATION[12]

- For autologous IV use only. Confirm patient identity matches cassette and infusion bag prior to infusion.
- Ensure tocilizumab (at least 2 doses) and emergency equipment are available prior to infusion and during recovery period.
- Administer infection prophylaxis as clinically indicated.
    - Do not administer to patients with clinically significant active systemic infection or inflammatory disorders.
- Premedication - Premedicate with acetaminophen 650 mg orally and diphenhydramine 12.5 mg IV or 25-50mg orally ~60 minutes prior to axi-cel infusion. Avoid prophylactic systemic corticosteroids as they may interfere with axi-cel activity.
- Administer at a REMS-certified healthcare facility.

Indication	Dosing
Relapsed or refractory Follicular Lymphoma IV	● A treatment course consists of lymphodepleting chemotherapy (with fludarabine and cyclophosphamide) on the 5th, 4th, and 3rd day prior to axi-cel infusion. ● **Target dose: 2 x 10^6 chimeric antigen receptor (CAR)$^+$ viable T cells/kg** ● Maximum dose: 2 x 10^8 CAR$^+$ viable T cells
Relapsed or refractory Large B-cell Lymphoma IV	

Geriatric

- Refer to adult dosing.

Pediatric

- The safety and efficacy in patients under 18 years of age has not been studied.

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[34]

In the phase 2 ZUMA-1 clinical study, Yescarta demonstrated high levels of durable response in patients with relapsed or refractory large B-cell lymphoma after two prior systemic therapies who received CAR T-cell therapy with axi-cel had, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events. Yescarta reported an objective response rate (ORR) of 82%, complete response (CR) rate of 52%, 6-month median duration of response of 8.1 months, 12-month duration of

response of 11.1 months, 12-month progression-free survival (PFS) of 5.8 months, 15-month PFS of 49%, 6-month overall survival (OS) of 78%, 12-month OS of 59%, and 18-month OS of 52%.

In the phase 2 ZUMA-5 clinical study, Yesarta had considerable and durable clinical benefit in patients with indolent non-Hodgkin's Lymphoma, with a manageable safety profile. Axi-cel reported an overall response rate of 92% (94% in FL, 85% in MZL), complete response (CR) rate of 76% (80% in FL, 60% in MZL), estimated 12-month median duration of response (DOR) rate of 72%, estimated 12-month progression-free survival (PFS) rate of 74%, and estimated 12-month median overall survival (OS) rate of 93%.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS[12]

Black Box Warnings

- Cytokine Release Syndrome (CRS)
    - Grade 3 or 4 CRS reactions have occurred.
    - Median time to onset: 2 to 4 days
    - Median duration: 6 to 7 days
    - Management with tocilizumab and corticosteroids
- Neurologic Toxicities
    - Grade 3 or higher neurotoxicity's have occurred.
    - Median time to onset: 4 to 6 days
    - Median duration: 8 to 17 days
    - Most neurotoxicity's occurred within the first 8 weeks following infusion.
- 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 axi-cel infusion. Unresolved (day 30) grade 3 or 4 cytopenia's included neutropenia, thrombocytopenia, and anemia.
- Hepatitis B virus reactivation
    - Reactivation (sometimes resulting in fulminant hepatitis, hepatic failure, and death) can occur in patients treated with medication directed against B cells.
- Hypersensitivity
    - Serious hypersensitivity reactions, including anaphylaxis, may occur due to dimethyl sulfoxide or residual gentamicin in axi-cel.
- Hypogammaglobulinemia and B-cell aplasia
- Infections
    - Serious infections (including life-threatening infections) occurred in patients after axi-cel infusion, including $\geq$ grade 3 infections. Viral, bacterial, fungal, and unknown pathogen infections were reported. Neutropenic fever has been observed after axi-cel infusion and may occur concurrently with CRS. Life-threatening and fatal opportunistic infections can occur in patients who are immunosuppressed. Opportunistic infections reported include disseminated fungal infections and viral reactivation. Consider the possibility of HHV06 encephalitis and PML in immunosuppressed patients with neurologic events and perform appropriate diagnostic evaluations.
- Secondary malignancies

ADVERSE REACTIONS[5]

Common

- Cardiovascular: Cardiac dysrhythmia (21% to 23%), Hypotension (51% to 57%), Tachycardia (44% to 57%)
- Gastrointestinal: Constipation (23% to 28%), Decrease in appetite (26% to 44%), Diarrhea (29% to 38%), Nausea (34% to 40%), Vomiting (24% to 26%)
- Neurologic: Dizziness (20% to 21%), Encephalopathy (49% to 57%), Headache (44% to 45%), Tremor (31%)
- Respiratory: Cough (25% to 30%), Hypoxia (23% to 32%)
- Other: Fatigue (46% to 49%), Fever (85% to 86%), Shivering (29% to 40%)

Serious

- See "Contraindications, Warnings, and Precautions" above.
- Other
    - Cardiovascular: Capillary leak syndrome (3%)
    - Immunologic: Hemophagocytic lymphohistiocytosis, Macrophage activation syndrome
    - Neurologic: Cerebral edema, Leukoencephalopathy, Seizure (2% to 4%)

Dose Adjustments for Toxicity[12]

Cytokine Release Syndrome

CRS Grade	Tocilizumab	Corticosteroids
Grade 1: symptomatic treatment only	If not improving after 24 hours, consider managing as per grade 2.	If not improving after 3 days, administer 1 dose of dexamethasone 10 mg IV.
Grade 2: symptoms require and respond to moderate intervention	Administer tocilizumab 8 mg/kg IV over 1h; may repeat every 8h if no clinical improvement. If improving, D/C tocilizumab.	Administer dexamethasone 10 mg IV once daily. If improving, manage as per grade 1 and continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.
Grade 3: symptoms require and respond to aggressive intervention	Per grade 2 If improving, manage as appropriate grade above.	Administer dexamethasone 10 mg IV 3 times daily. If improving, manage as appropriate grade above and continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, manage as grade 4..
Grade 4: life-threatening symptoms	Per grade 2 If improving, manage as appropriate grade above.	Administer methylprednisolone 1g IV daily for 3 days. If improving, manage as per grade 1 and continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, consider methylprednisolone 1 g 2-3 times daily, or alternate therapy.

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

Neurotoxicity

Grade	Concurrent CRS	No Concurrent CRS
1	Administer tocilizumab per previous (CRS) table for management of grade 1 CRS. In addition, administer 1 dose of dexamethasone 10 mg IV. If not improving after 2 days, repeat dexamethasone IV.	Administer 1 dose of dexamethasone 10 mg IV. If not improving after 2 days, repeat dexamethasone 10 mg IV.
	Consider non-sedating anti-seizure medication (eg. Keppra) for seizure prophylaxis.	
2	Administer tocilizumab per previous (CRS) table for management of grade 2 CRS. Administer 1 dose of dexamethasone 10 mg IV 4 times daily. If improving, continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.	Administer dexamethasone 10 mg IV 4 times daily. If improving, continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.
	Consider non-sedating anti-seizure medication (eg. Keppra) for seizure prophylaxis.	
3	Administer tocilizumab per previous (CRS) table for management of grade 2 CRS. In addition, administer methylprednisolone 1 g IV once daily. If improving, manage as appropriate grade above and continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, manage as grade 4.	Administer methylprednisolone 1 g IV once daily. If improving, manage as appropriate grade above and continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, manage as grade 4.
	Consider non-sedating anti-seizure medication (eg. Keppra) for seizure prophylaxis.	
4	Administer tocilizumab per previous (CRS) table for management of grade 2 CRS. In addition, administer methylprednisolone 1 g IV twice daily. If improving, manage as appropriate grade above and continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, consider methylprednisolone 1 g IV 3 times daily or alternate therapy.	Administer methylprednisolone 1 g IV twice daily. If improving, manage as appropriate grade above and continue corticosteroids until severity is ≤ grade 1, then quickly taper as clinically appropriate. If not improving, consider methylprednisolone 1 g IV 3 times daily or alternate therapy.
	Consider non-sedating anti-seizure medication (eg. Keppra) for seizure prophylaxis.	

Other Toxicities

Toxicity	Management
Hypogammaglobulinemia	Manage with IV globulin replacement and with infection precautions and antibiotic and/or antiviral prophylaxis as indicated.
Infection	Administer prophylactic antimicrobials prior to axi-cel according to standard institutional guidelines. Manage infection appropriately.
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]

YESCARTA and TECARTUS have a combined REMS Program.

- Hospitals and their associated clinics must enroll in the YESCARTA and TECARTUS REMS Program to be able to dispense either medication.
- All relevant staff involved in prescribing, dispensing, or administering of YESCARTA and/or TECARTUS are trained on REMS Program requirements and must successfully complete a REMS Program Knowledge Assessment.
- Ensure that the hospital and its associated clinics have a minimum of 2 doses of tocilizumab available on-site for each patient and are ready for immediate administration (within 2 hours)
- Prior to patient discharge, provide patients/caregivers with the Patient Wallet Card and instruct patients to remain within proximity (2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following infusion.
- Further information is available at www.yescartatecartusrems.com or contact Kite Pharma, Inc. at 1-844-454-KITE.

MAJOR INTERACTIONS[1]

Drug-Drug (Risk X - Avoid Combination)

- Immunizations
    - Live Vaccines - immunosuppressants may enhance the adverse/toxic effect of live vaccines. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated less than 2 weeks before, revaccinate at least 3 months after discontinuation. Immunosuppressants may diminish therapeutic effects 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.
- 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

- None

MONITORING REQUIREMENTS[12]

- Screen for HBV, HCV, and HIV prior to collection of cells for manufacturing.
- Monitor CBC prior to and after administration.
- Evaluate pregnancy status prior to use.
- Monitor immunoglobulin levels (IgG) after treatment.
- Monitor patients daily (for signs/symptoms of cytokine release syndrome and neurotoxicity) at the health care facility for at least 7 days after cell infusion. Patients should remain within proximity of the facility for at least 4 weeks after infusion.

- Monitor for signs/symptoms of hypersensitivity, infections, and secondary malignancies.

PREGNANCY/BREASTFEEDING[12]

- Evaluate pregnancy status prior to therapy in females of reproductive potential; pregnancy testing is recommended prior to therapy in sexually active females of reproductive potential.
- The duration of contraception needed following axi-cel administration is not known.
- Treatment with axi-cel is not recommended during pregnancy. If placental transfer were to occur, fetal toxicity, including B-cell lymphocytopenia, may occur.
- Potential pregnancies (following treatment) should be discussed with the provider.
- It is not known if axi-cel is present in breast milk.

MEDICATION SAFETY ISSUES[1]

Sound/Look Alike issues

- Axicabtagene ciloleucel may be confused with brexucabtagene autoleucel, idecabtagene vicleucel, lisocabtagene maraleucel, sipuleucel-T, tisagenlecleucel.
- Yescarta may be confused with Tecartus, Yervoy.

High Alert Medication

- N/A

SPECIAL STORAGE PRECAUTIONS[12]

- Store frozen suspension in the vapor phase of liquid nitrogen ($\leq$ -150°C).
- After thawing, it may be stored for up to 3 hours at room temperature of 20 to 25°C.

SPECIAL HANDLING/ADMINISTRATION[12]

- Apply universal precautions and local biosafety guidelines for handling and disposal.
- Before thawing, inspect the infusion bag(s) for breaches of container integrity (i.e breaks or cracks); contact the manufacturer if compromised.
- To thaw, place the bag inside a second sterile bag and thaw at ~37°C 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 entire contents of bag within 30 minutes either by gravity or peristaltic pump. After completion of the infusion, rinse the tubing with NS at the same infusion rate to ensure cell product delivery.
- Do not use a leukodepletion filter. A central line may be used for administration.

COST AND REIMBURSEMENT INFORMATION[7]

Cost (Estimated WAC)	$373,000
Medical/Pharmacy Benefit	Medical
Inpatient/Outpatient	Outpatient
HCPCS Code	Q2041 axicabtagene ciloleucel - Axicabtagene ciloleucel, up to 200 million autologous anti-CD19 CAR$^+$ T cells
NOC Code Billing Guide	See IPD CODESOURxCE

PATIENT ASSISTANCE AVAILABILITY[8]

- Kite Konnect® offers assistance programs that provide reimbursement support by helping with benefits investigations, claims appeals information, and potential sources of support for eligible uninsured and underinsured patients.
- Additional information at www.kitekonnect.com or contact 1-844-454-KITE [5483].

REFERENCES

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