GENE AND CELLULAR THERAPY - CAR-T Cell Immunotherapy

Brexucabtagene autolecuel (Brexu-cel, Tecartus; Kite Pharma, a Gilead Sciences Company)
Original FDA Approval Date: MCL - 7/24/2020; ALL - 10/01/2021

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

AVAILABLE FORMULATIONS[1]
Suspension for intravenous infusion [contains DMSO and albumin human]

INDICATIONS
FDA Approved[12]
- Treatment of relapsed or refractory mantle cell lymphoma (MCL) in adults.
- Treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
- It is also being studied in chronic lymphocytic leukemia (CLL) and B-cell non-Hodgkin lymphoma.

Off-Label uses[3]
- None

DESCRIPTION AND CLINICAL PHARMACOLOGY[13]
Brexu-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). 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[13]

Onset	Median time to initial response: 1 month. Median time to complete response: 3 months.
Time to Peak	Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 14 days. The median peak anti-CD19 CAR T cell level in patients who responded was 102.4 cells/mCL compared to 12 cells/mcL in nonresponders.
Duration / Expansion	Anti-CD19 CAR T cells displayed initial rapid expansion followed by a decline to near baseline levels by 3 months post brexu-cel infusion. The number of anti-CD19 CAR T cells in the blood was positively associated with ORR..

DOSING AND ADMINISTRATION[14]

- 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 ~30-60 minutes prior to brexu-cel infusion. Avoid prophylactic dexamethasone or other systemic corticosteroids as they may interfere with brexu-cel activity.
- Administer at a REMS-certified healthcare facility.

Indication	Dosing
Relapsed or refractory mantle cell lymphoma (MCL) - IV	● A treatment course of lymphodepleting chemotherapy, with fludarabine and cyclophosphamide, on the fifth, fourth, and third day prior to brexu-cel infusion. ○ Confirm availability of brexu-cel prior to initiating lymphodepleting chemotherapy. ● **Target dose: 2 x 10^6 chimeric antigen receptor $(CAR)^+$ viable T cells/kg** ● Maximum dose: 2 x 10^8 CAR^+ T cells.

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[56]

In the phase 2 ZUMA-2 study, Tecartus showed that a single infusion induces durable remission in patients with relapsed or refractory mantle-cell lymphoma after the failure of BTK inhibitor therapy. Serious and life-threatening toxic events occurred that are largely consistent with those reported in previous studies of anti-CD19 CAR T-cell therapies in patients with aggressive B-cell lymphoma. Brexu-cel reported an overall response rate (ORR) of 93%, complete response (CR) rate of 67%, progression-free survival (PFS) of 61% at 12 months, and overall survival (OS) of 83% at 12 months.

In the phase 2 ZUMA-3 study, Tecartus as a single infusion showed induction of durable remission with manageable safety in heavily pretreated adults with relapsed or refractory B-precursor acute lymphoblastic leukemia. Brexu-cel reported an overall response rate (ORR) of 71%, complete response (CR) rate of 56%, median duration of remission of 12.8 months, median relapse-free survival (RFS) of 11.6 months in all patients and 14.3 months in responders, 6-month RFS rate of 58%, and a median overall survival (OS) of 18.2 months with a 12-month rate of 71%.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS[145]

Black Box Warnings

- Cytokine Release Syndrome
    - Grade 1 or 2 occurred in 76%, grade 3 or higher occurred in 15%
    - Median time to onset: 2 days
    - Median duration: 11days
    - Tocilizumab use: 59%, glucocorticoids use: 22%, and vasopressor use: 16%
- Neurologic Toxicities
    - Grade 1 or 2 occurred in 32%, grade 3 or higher occurred in 31%
    - Median time to onset: 7 days
    - Median duration: 12 days
    - Tocilizumab use: 26%, glucocorticoids use: 38%
- REMS program

Contraindications

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

Warnings and Precautions

- Cytopenia's
    - Prolonged cytopenia's may occur for several weeks after lymphodepleting chemotherapy and brexu-cel infusion. Unresolved grade 3 and 4 cytopenia's included thrombocytopenia, neutropenia, 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 brexu-cel.
- Hypogammaglobulinemia and B-cell aplasia
- Infections
    - Serious infections have occurred with brexu-cel; infections occurred in 50% after infusion, including grade 3 or higher in 30%. Infections include bacterial, viral, fungal and infection with unspecified pathogens. Neutropenic fever has been observed and may be concurrent with CRS. Life-threatening and fatal infections, including disseminated fungal infections and viral reactivation have been reported in immunosuppressed patients.
- Secondary malignancies

ADVERSE REACTIONS[7]

Common

- Cardiovascular: Edema (35%), Hypotension (57%)
- Dermatologic: Rash (22%), Shivering (41%)
- Gastrointestinal: Constipation (29%), Decrease in appetite (26%), Diarrhea (28%), Nausea (35%)
- Musculoskeletal: Musculoskeletal pain (37%)
- Neurologic: Insomnia (21%)
- Respiratory: Cough (38%), Dyspnea (24%), Hypoxia (40%), Pleural effusion (21%)
- Other: Fatigue (48%), Fever (94%)

Serious

- See "Contraindications, Warnings, and Precautions" above.
- Other

- Neurologic: Aphasia (20%), Encephalopathy (51%), Headache (35%), Tremor (38%)
- Psychiatric: Delirium (16%)

Dose Adjustments for Toxicity[14]

Cytokine Release Syndrome

CRS Grade	Tocilizumab	Corticosteroids
Grade 1: symptomatic treatment only	If not improving after 24 hours, administer tocilizumab 8 mg/kg IV over 1h (max 800 mg/dose).	Not indicated.
Grade 2: symptoms require and respond to moderate intervention	Administer tocilizumab 8 mg/kg IV over 1h; may repeat every 8h PRN if not responsive to IV fluids or increasing supplemental oxygen. If improving, D/C tocilizumab.	If no improvement within 24 h after initiating tocilizumab, manage as per grade 3. If improving, taper corticosteroids.
Grade 3: symptoms require and respond to aggressive intervention	Administer tocilizumab as per grade 2. If improving, D/C tocilizumab.	Administer methylprednisolone 1 mg/kg IV BID or equivalent dexamethasone (eg, 10 mg IV q6h) until grade 1, then taper corticosteroids. If improving, manager as grade 2. If not improving, manage as grade 4.
Grade 4: life-threatening symptoms	Administer tocilizumab as per grade 2. If improving, D/C tocilizumab.	Administer methylprednisolone 1g IV daily for 3 days; if improving, taper corticosteroids and manage as grade 3. If not improving, consider alternate immunosuppressants.

*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.	Supportive care.
2	Administer tocilizumab per previous (CRS) table for management of grade 2 CRS. If not improving within 24 h of initiating tocilizumab, administer dexamethasone 10 mg IV q6h until ≤ grade 1, then taper corticosteroids. If improving, D/C tocilizumab. If still not improving, manage as grade 3.	Administer dexamethasone 10 mg IV q6h until ≤ grade 1. If improving, taper corticosteroids.
	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 dexamethasone 10 mg IV q6h until ≤ grade 1, then taper corticosteroids. If improving, D/C tocilizumab and manage as grade 2. If not improving, manage as grade 4.	Administer dexamethasone 10 mg IV q6h until ≤ grade 1, then taper corticosteroids. 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. Administer methylprednisolone 1 g IV daily for 3 days. If improving, manage as grade 3. If not improving, consider alternate immunosuppressants.	Administer methylprednisolone 1 g IV daily for 3 days. If improving, manage as grade 3. If not improving, consider alternate immunosuppressants.
	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.
Neutropenic fever	Evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as clinically indicated.

RISK EVALUATION AND MITIGATION STRATEGIES[8]

- 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
    - Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during brexu-cel treatment, and until immune recovery following treatment with brexu-cel. Immunization with live viral vaccines during or following brexu-cel has not been studied.
    - 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.
- Corticosteroids - avoid use of prophylactic corticosteroids.

- 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[14]
- Screen for HBV, HCV, and HIV prior to collection of cells for manufacturing.
- Monitor CBC (blood counts) 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 hypersensitivity, infection, or neutropenic fever.
- Monitor (life-long) for secondary malignancies.

PREGNANCY/BREASTFEEDING[14]
- Evaluate pregnancy status prior to administration.
- Based on mechanism of action, in utero exposure to brexu-cel may cause fetal harm.
- It is not known if Brexu-cel is present in breast milk.
    - Consider the risk of infant exposure, the benefits of breastfeeding the infant, and the benefits of treatment to the mother.

MEDICATION SAFETY ISSUES[1]
Sound/Look Alike issues
- Brexu-cel may be confused with axicabtagene ciloleucel, brentuximab vedotin, idecabtagene vicleucel, lisocabtagene maraleucel, sipuleucel-T, tisagenlecleucel.
- Tecartus may be confused with Yescarta.

High Alert Medication
- N/A

SPECIAL STORAGE PRECAUTIONS[14]
- Store frozen suspension in the vapor phase of liquid nitrogen (-150°C or less [-238°F or less]).
- After thawing, it may be stored for up to 3 hours at room temperature of 20°C to 25°C (68°F to 77°F).

SPECIAL HANDLING/ADMINISTRATION[14]
- Brexu-cel contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal.
- Inspect patient-specific infusion bags for breaches in container integrity (such as breaks or cracks) prior to thawing.

    - To thaw: place the infusion bag inside a second sterile bag. Thaw at ~37°C (~98.6°F) using a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix contents of the thawed infusion bag to disperse cellular material clumps; inspect for visible cell clumps; if visible cell clumps remain, gently mix the contents of the bag (small clumps of cellular material should disperse with gentle manual mixing). Do not wash, spin down, and/or re-suspend brexu-cel in new media prior to infusion.
    - Coordinate timing of administration with thawing
- Prime the tubing with NS prior to infusion. Infuse the entire contents of the bag within 30 minutes either by gravity or a peristaltic pump (infusion bag volume is ~68 mL). A central line is preferred for infusion. Gently agitate the bag during infusion to prevent cell clumping. After completion of the infusion, rinse the tubing with NS at the same infusion rate to ensure complete cell product delivery.
- Do not use a leukodepleting filter.

COST AND REIMBURSEMENT INFORMATION[3]

Cost (Estimated WAC)	$373,000 for a single infusion
Sales Projections (Estimated)	$197 million in peak sales
Medical/Pharmacy Benefit	Medical
Inpatient/Outpatient	Inpatient
Reimbursement Code	J9999 (NOC) not otherwise classified, antineoplastic drugs C9399 (NOC) [hospital outpatient use]
NOC Code Billing Guide	See IPD CODESOURxCE

PATIENT ASSISTANCE AVAILABILITY[9]

- 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].

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