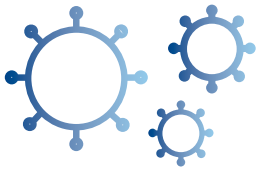
Breyanzi® (lisocabtagene maraleucel) suspension for IV infusion

A CAR T Cell Therapy for Adults with Relapsed or Refractory Large B-cell Lymphoma

About *Breyanzi*®

Indications: *Breyanzi* is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:



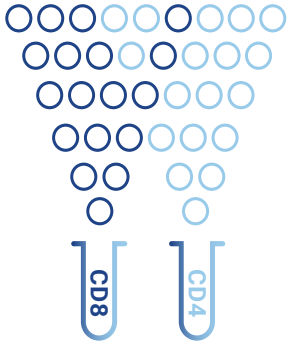
- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- Relapsed or refractory disease after two or more lines of systemic therapy.[1]

Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma.[1]

Select Important Safety Information[1]

BOXED WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving *Breyanzi*. Do not administer *Breyanzi* to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving *Breyanzi*, including concurrently with CRS, after CRS resolution or in the absence of CRS. Monitor for neurologic events after treatment with *Breyanzi*. Provide supportive care and/or corticosteroids as needed.**
- ***Breyanzi* is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the *Breyanzi* REMS.**



The U.S. Food and Drug Administration (FDA) approval of *Breyanzi* in the second-line setting was based on data from the Phase 3 global, randomized, open-label, parallel group multicenter TRANSFORM trial of 182 transplant eligible patients with high-risk, relapsed or refractory LBCL after failure of first-line therapy who were randomized 1:1 to receive a single infusion of *Breyanzi* or standard therapy consisting of chemoimmunotherapy followed by high-dose therapy and autogolous HSCT. The approval was also supported by the Phase 2 open-label, single-arm PILOT study, which included 61 adults with primary relapsed or refractory LBCL who were transplant ineligible.

Breyanzi is a CD19-directed CAR T cell therapy with a defined and purified composition and 4-1BB costimulatory domain. *Breyanzi* is administered as a defined composition to reduce variability of the CD8 and CD4 component dose. The 4-1BB signaling enhances the expansion and persistence of *Breyanzi*. *Breyanzi* offers a one-time individualized treatment, which includes leukapheresis, manufacturing, administration, and adverse event monitoring.[1]

The FDA approval of *Breyanzi* in the third-line plus setting was based on data from the Phase 1 open-label, multicenter TRANSCEND NHL 001 trial of 268 patients with relapsed or refractory LBCL who had received two or more lines of prior systemic therapy. TRANSCEND NHL 001, the largest pivotal trial in third-line plus relapsed or refractory large B-cell lymphoma included patients with a broad range of histologies.

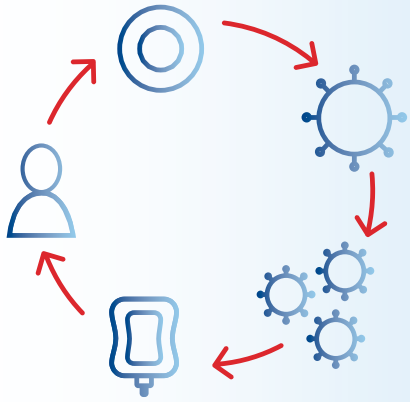
Treatment with *Breyanzi*

Administered in either an inpatient or outpatient setting at the prescriber's discretion, *Breyanzi* is suspended in one to four single-dose vials of each component. For LBCL after one line of therapy, a single dose of *Breyanzi* contains 90 to 110 x 10^6 CAR-positive viable T cells.[1] For LBCL after two or more lines of therapy, a single dose of *Breyanzi* contains 50 to 110 × 10^6 CAR-positive viable T cells.[1]

Breyanzi is prepared from a patient's own T cells, removed through a process called apheresis or leukapheresis in which blood is withdrawn and T cells are separated from other blood components.[2]

The collected T cells are shipped to a specialized cell therapy manufacturing facility where they undergo genetic "reprogramming" to become CAR T cells. Receptors (or hooks) are added to the T cells to help recognize and target CD-19 expressing cells, including normal and cancer cells. The CAR T cells are then multiplied to create the appropriate dose consisting of millions of CAR T cells, which then undergo rigorous testing and quality control before being shipped back to the patient for infusion at a CAR T cell treatment center.[3]

After the patient receives *Breyanzi*, they are monitored daily at the CAR T cell treatment center during the first week and must remain within proximity of the CAR T cell treatment center for at least four weeks for monitoring (post-infusion monitoring period).



Learn more at **www.*Breyanzi*.com** and **www.*Breyanzi*REMS.com**

Patient and Care Team Support

Bristol Myers Squibb is supporting the patient and physician treatment experience by providing:

- Disposable wearable technology during the initial post-infusion monitoring period, which can help patients track their temperature through a smartphone when away from the treatment center. Patients are instructed to call their doctor if their temperature is 100.4˚F or higher.
- Cell Therapy 360, a digital service platform, which optimizes access to relevant information, manufacturing updates, patient and caregiver support, and outpatient management resources to support patients.
- Resources that help provide access to a Bristol Myers Squibb CAR T cell therapy, including *Breyanzi*.

Important Safety Information

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- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving *Breyanzi*, including concurrently with CRS, after CRS resolution or in the absence of CRS. Monitor for neurologic events after treatment with *Breyanzi*. Provide supportive care and/or corticosteroids as needed.**
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Cytokine Release Syndrome

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with *Breyanzi*. Among patients receiving *Breyanzi* for LBCL (N=418), CRS occured in 46% (190/418) of patients, including ≥ Grade 3 CRS (Lee grading system) in 3.1% of patients. In patients receiving *Breyanzi* after two or more lines of therapy for LBCL, CRS occurred in 46% (122/268), including ≥ Grade 3 CRS in 4.1% of patients. One patient had fatal CRS and 2 had ongoing CRS at time of death. The median time to onset was 5 days (range: 1 to 15 days). CRS resolved in 98% with a median duration of 5 days (range: 1 to 17 days). In patients receiving *Breyanzi* after one line of therapy for LBCL, CRS occurred in 45% (68/150), including Grade 3 CRS in 1.3% of patients. The median time to onset was 4 days (range: 1 to 63 days). CRS resolved in all patients with a median duration of 4 days (range: 1 to 16 days).

Important Safety Information (cont'd)

Cytokine Release Syndrome (cont'd)

The most common manifestations of CRS (≥10%) included fever (94%), hypotension (42%), tachycardia (28%), chills (23%), hypoxia (16%), and headache (12%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, diffuse alveolar damage, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).
Ensure that 2 doses of tocilizumab are available prior to infusion of *Breyanzi*.

Of the 418 patients who received *Breyanzi* for LBCL, 23% received tocilizumab and/or a corticosteroid for CRS, including 10% who received tocilizumab only and 2.2% who received corticosteroids only.

Neurologic Toxicities

Neurologic toxicities that were fatal or life-threatening, including immune effector cell-associated neurotoxicity syndrome (ICANS), occurred following treatment with *Breyanzi*. Serious events including cerebral edema and seizures occurred with *Breyanzi*. Fatal and serious cases of leukoencephalopathy, some attributable to fludarabine, also occurred. In patients receiving *Breyanzi* after two or more lines of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred. In 35% (95/268), including ≥ Grade 3 in 12% of patients. Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death. The median time to onset of neurotoxicity was 8 days (range: 1 to 46 days). Neurologic toxicities resolved in 85% with a median duration of 12 days (range: 1 to 87 days). In patients receiving *Breyanzi* after one line of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred in 27% (41/150) of patients, including Grade 3 cases in 7% of patients. The median time to onset of neurologic toxicities was 8 days (range: 1 to 63 days). The median duration of neurologic toxicity was 6 days (range: 1 to 119 days).

In all patients combined receiving *Breyanzi* for LBCL, neurologic toxicities occurred in 33% (136/418), including ≥ Grade 3 cases in 10% of patients. The median time to onset was 8 days (range: 1 to 63), with 87% of cases developing by 16 days. Neurologic toxicities resolved in 85% of patients with a median duration of 11 days (range: 1 to 119 days). Of patients developing neurotoxicity, 77% (105/136) also developed CRS.
The most common neurologic toxicities (≥ 5%) included encephalopathy (20%), tremor (13%), aphasia (8%), headache (6%), dizziness (6%), and delirium (5%).

CRS and Neurologic Toxicities Monitoring

Monitor patients daily for at least 7 days following *Breyanzi* infusion at a REMS-certified healthcare facility for signs and symptoms of CRS and neurologic toxicities and assess for other causes of neurological symptoms. Monitor patients for signs and symptoms of CRS and neurologic toxicities for at least 4 weeks after infusion and treat promptly. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated. Manage neurologic toxicity with supportive care and/or corticosteroid as needed. Counsel patients to seek immediate medical attention should signs or symptoms of CRS or neurologic toxicity occur at any time.

Breyanzi REMS

Because of the risk of CRS and neurologic toxicities, *Breyanzi* is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the *Breyanzi* REMS. The required components of the *Breyanzi* REMS are:

- Healthcare facilities that dispense and administer *Breyanzi* must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab.
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after *Breyanzi* infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer *Breyanzi* are trained on the management of CRS and neurologic toxicities.

Further information is available at www.*Breyanzi*REMS.com, or contact Bristol-Myers Squibb at 1-888-423-5436.

Hypersensitivity Reactions

Allergic reactions may occur with the infusion of *Breyanzi*. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO).

Serious Infections

Severe infections, including life-threatening or fatal infections, have occurred in patients after *Breyanzi* infusion. In patients receiving *Breyanzi* for LBCL, infections of any grade occurred in 36% with Grade 3 or higher infections occurring in 12% of all patients. Grade 3 or higher infections with an unspecified pathogen occurred in 7%, bacterial infections occurred in 4.3%, viral infections in 1.9% and fungal infections in 0.5%.

Febrile neutropenia developed after *Breyanzi* infusion in 8% of patients with LBCL. Febrile neutropenia may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated. Monitor patients for signs and symptoms of infection before and after *Breyanzi* administration and treat appropriately. Administer prophylactic antimicrobials according to standard institutional guidelines.

Important Safety Information (cont'd)

Serious Infections (cont'd)

Avoid administration of *Breyanzi* in patients with clinically significant active systemic infections.

Viral reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. In patients who received *Breyanzi* for LBCL, 15 of the 16 patients with a prior history of HBV were treated with concurrent antiviral suppressive therapy. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing. In patients with prior history of HBV, consider concurrent antiviral suppressive therapy to prevent HBV reactivation per standard guidelines.

Prolonged Cytopenias

Patients may exhibit cytopenias not resolved for several weeks following lymphodepleting chemotherapy and *Breyanzi* infusion. Grade 3 or higher cytopenias persisted at Day 29 following *Breyanzi* infusion in 36% of patients with LBCL and included thrombocytopenia in 28%, neutropenia in 21%, and anemia in 6%. Monitor complete blood counts prior to and after *Breyanzi* administration.

Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with *Breyanzi*. In patients receiving *Breyanzi* for LBCL, hypogammaglobulinemia was reported as an adverse reaction in 11% of patients. Hypogammaglobulinemia, either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion, was reported in 28% of patients. Monitor immunoglobulin levels after treatment with *Breyanzi* and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement as clinically indicated.

Live vaccines: The safety of immunization with live viral vaccines during or following *Breyanzi* treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during *Breyanzi* treatment, and until immune recovery following treatment with *Breyanzi*.

Secondary Malignancies

Patients treated with *Breyanzi* may develop secondary malignancies. Monitor lifelong for secondary malignancies. In the event that a secondary malignancy occurs, contact Bristol-Myers Squibb at 1-888-805-4555 for reporting and to obtain instructions on collection of patient samples for testing.

Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving *Breyanzi* are at risk for developing altered or decreased consciousness or impaired coordination in the 8 weeks following *Breyanzi* administration. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks.

Adverse Reactions

The most common nonlaboratory adverse reactions (incidence ≥ 30%) are fever, CRS, fatigue, musculoskeletal pain, and nausea.

The most common Grade 3-4 laboratory abnormalities (≥ 30%) include lymphocyte count decrease, neutrophil count decrease, platelet count decrease, and hemoglobin decrease.

Click here for full Prescribing Information, including **Boxed WARNINGS**.

References
1. *Breyanzi* Prescribing Information. Bristol Myers Squibb; June 2022.
2. Cleveland Clinic. CAR T-Cell Therapy: Procedure Details. Available at: https://my.clevelandclinic.org/health/treatments/17726-car-t-cell-therapy/procedure-details. Accessed April 2022.
3. Leukemia and Lymphoma Society. Chimeric Antigen Receptor (CAR) T-Cell Therapy. Available at: https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy. Accessed April 2022.

Breyanzi (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION