



U.S. Food and Drug Administration Approves Bristol Myers Squibb's *Breyanzi* (lisocabtagene maraleucel), a New CAR T Cell Therapy for Adults with Relapsed or Refractory Large B-cell Lymphoma

Breyanzi demonstrated a 73% overall response rate and 54% complete response (CR) rate in the largest pivotal trial in 3L+ LBCL, TRANSCEND NHL 001 trial

Breyanzi demonstrated sustained responses in patients who achieved a CR with median duration of response not reached

Grade ≥ 3 cytokine release syndrome and Grade ≥ 3 neurologic toxicities following Breyanzi treatment occurred in 4% and 12% of patients, respectively

(PRINCETON, N.J., February 5, 2021) -- [Bristol Myers Squibb](#) (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has approved *Breyanzi* (lisocabtagene maraleucel; liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, 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. *Breyanzi* is not indicated for the treatment of patients with primary central nervous system lymphoma.¹ *Breyanzi* is a CD19-directed CAR T cell therapy with a defined 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 potentially definitive treatment. A single dose of *Breyanzi* contains 50 to 110 x 10⁶ CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components). Please see the Important Safety Information section below, including **Boxed**

WARNINGS for *Breyanzi* regarding Cytokine Release Syndrome (CRS) and Neurologic Toxicities (NT).

“*Breyanzi*, a CAR T cell therapy, will have an important role in clinical practice, offering people living with relapsed or refractory large B-cell lymphoma the chance for sustained response with an individualized treatment experience,” said [Samit Hirawat, M.D.](#), chief medical officer, Bristol Myers Squibb. “Today’s FDA approval reflects our deep commitment to advancing cell therapy research, developing innovative treatments and supporting patients at every step of their treatment journey.”

Bristol Myers Squibb plans to manufacture *Breyanzi* for each individual patient at its state-of-the-art cellular immunotherapy manufacturing facility in Bothell, Washington. *Breyanzi* offers a 24-day target turnaround time, and inpatient or outpatient administration options. To help support broad patient access, Bristol Myers Squibb plans to launch *Breyanzi* across an expansive network of treatment centers. Treatment centers will be Risk Evaluation and Mitigation Strategy (REMS) certified to support the appropriate use of *Breyanzi*, which is available only through the *Breyanzi* REMS program. Healthcare facilities, including hospitals and associated outpatient clinics, must enroll and comply with REMS requirements and be trained on the management of CRS and NT. Bristol Myers Squibb is also supporting the patient and physician treatment experience by providing 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. BMS will offer patients disposable wearable technology during the initial post-infusion monitoring period, which will help them track their temperature in real time through a smartphone when away from the treatment center.

“In TRANSCEND NHL 001, *Breyanzi* produced sustained responses in a significant proportion of patients with relapsed or refractory large B-cell lymphoma. TRANSCEND also demonstrated feasibility of outpatient administration, which is meaningful for patients, physicians and the healthcare system,” said Jeremy Abramson, M.D., M.M.Sc., director of the lymphoma program at Massachusetts General Hospital and principal investigator for TRANSCEND NHL 001. “With this approval, we now have an

important new treatment option for patients with relapsed or refractory large B-cell lymphoma who have undergone at least two prior lines of systemic therapy.”

Diffuse large B-cell lymphoma (DLBCL) is a rapidly growing, aggressive disease and the most common form of non-Hodgkin lymphoma (NHL), accounting for one out of every three cases diagnosed.² Seventy-three percent of patients will not respond to or will relapse following second-line treatment or later.³ For patients who relapse or do not respond to initial therapies, conventional treatment options that provide sustained responses are limited and median life expectancy is about six months.³ The goal of treatment in DLBCL is curative intent with definitive therapy.³ Additional options are needed in R/R DLBCL to deliver sustained responses to these patients.

“People battling relapsed or refractory large B-cell lymphoma continue to face a challenging treatment journey, both physically and emotionally,” said Meghan Gutierrez, chief executive officer, Lymphoma Research Foundation. “*Breyanzi* is an innovative treatment that offers a new option for patients, and another reason for this community to maintain hope for the future.”

Bristol Myers Squibb offers various programs and resources to address the needs of patients and caregivers, and provide support that allows for access to therapies, including *Breyanzi*.

Breyanzi has been granted Priority Medicines (PRIME) designation for R/R DLBCL in the European Union and a Marketing Authorization Application (MAA) is currently under review by the European Medicines Agency.

TRANSCEND NHL 001 Pivotal Trial Results

The FDA approval of *Breyanzi* is based on data from the TRANSCEND NHL 001 (017001) trial in which 268 patients with R/R LBCL received *Breyanzi*, the largest pivotal trial in third-line plus R/R LBCL that included patients with a broad range of histologies and high-risk disease. In the trial, *Breyanzi* was administered in the inpatient and outpatient settings.¹

In the study, 192 patients were treated with *Breyanzi* at the dose of 50 to 110 x 10⁶ CAR-positive viable T cells and evaluated for efficacy. Of these patients, 73% achieved a response (95% CI: 67%-80%), including 54% who had minimal or no detectable

lymphoma remaining following treatment (CR; 95% CI: 47%-61%) and 19% who achieved a partial response (PR; 95% CI: 14%-26%). Median duration of response was 16.7 months in all responders (95% CI: 5.3 - NR), and for patients who achieved a CR, median duration of response was not reached (95% CI: 16.7 - NR); for patients with a best response of PR, median duration of response was 1.4 months (95% CI: 1.1 - 2.2). Of 104 patients treated with *Breyanzi* who achieved a best overall response of CR, 65% had remission lasting at least six months and 62% had remission lasting at least nine months.

In the study, 268 patients treated with *Breyanzi* were evaluated for safety. Any grade CRS occurred in 46% (122/268) of patients using the Lee grading system.⁴ Grade ≥ 3 CRS occurred in 4% (11/268) of patients. One patient had fatal CRS and two had ongoing CRS at the time of death. The most common manifestations of CRS included fever (93%), hypotension (49%), tachycardia (39%), chills (28%) and hypoxia (21%). The median duration of CRS was five days (range: 1-30 days) and median time to onset was five days (range: 1-15 days). Any grade neurologic toxicities (NT) occurred in 35% (95/268) of patients receiving *Breyanzi*. Grade ≥ 3 NT occurred in 12% (31/268) of patients. Three patients had fatal neurologic toxicity and seven had ongoing neurologic toxicity at time of death. The most common NT included encephalopathy (24%), tremor (14%), aphasia (9%), delirium (7%), headache (7%), ataxia (6%), and dizziness (6%). Neurologic toxicities resolved in 81 of 95 patients (85%), with a median duration of 12 days (range: 1-87 days). The median time to onset of the first event was eight days (range: 1-46 days).¹ Median duration of neurologic toxicity was 15 days (range: 1 to 785 days) in all patients, including those with ongoing neurologic events at the time of death or at data cutoff.

Serious adverse reactions occurred in 46% of patients. The most common nonlaboratory, serious adverse reactions ($>2\%$) were CRS, encephalopathy, sepsis, febrile neutropenia, aphasia, pneumonia, fever, hypotension, dizziness, and delirium. Fatal adverse reactions occurred in 4% of patients. The most common nonlaboratory adverse reactions of any grade ($\geq 20\%$) were fatigue, CRS, musculoskeletal pain, nausea, headache, encephalopathy, infections (pathogen unspecified), decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, vomiting, and edema.

Indication

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after two or more lines of systemic therapy, 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.

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.

Important Safety Information

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.

Cytokine Release Syndrome (CRS)

CRS, including fatal or life-threatening reactions, occurred following treatment with BREYANZI. CRS occurred in 46% (122/268) of patients receiving BREYANZI, including \geq Grade 3 (Lee grading system) CRS in 4% (11/268) 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 119 of 122 patients (98%) with a median

duration of 5 days (range: 1 to 17 days). Median duration of CRS was 5 days (range 1 to 30 days) in all patients, including those who died or had CRS ongoing at time of death.

Among patients with CRS, the most common manifestations of CRS include fever (93%), hypotension (49%), tachycardia (39%), chills (28%), and hypoxia (21%). 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. Sixty-one of 268 (23%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of BREYANZI. Twenty-seven (10%) patients received tocilizumab only, 25 (9%) received tocilizumab and a corticosteroid, and 9 (3%) received corticosteroids only.

Neurologic Toxicities

Neurologic toxicities that were fatal or life-threatening, occurred following treatment with BREYANZI. CAR T cell-associated neurologic toxicities occurred in 35% (95/268) of patients receiving BREYANZI, including \geq Grade 3 in 12% (31/268) of patients. Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death. The median time to onset of the first event was 8 days (range: 1 to 46 days). The onset of all neurologic events occurred within the first 8 weeks following BREYANZI infusion. Neurologic toxicities resolved in 81 of 95 patients (85%) with a median duration of 12 days (range: 1 to 87 days). Three of four patients with ongoing neurologic toxicity at data cutoff had tremor and one subject had encephalopathy. Median duration of neurologic toxicity was 15 days (range: 1 to 785 days) in all patients, including those with ongoing neurologic events at the time of death or at data cutoff.

Seventy-eight (78) of 95 (82%) patients with neurologic toxicity experienced CRS. Neurologic toxicity overlapped with CRS in 57 patients. The onset of neurologic toxicity was after onset of CRS in 30 patients, before CRS onset in 13 patients, same day as CRS onset in 7 patients, and same day as CRS resolution in 7 patients.

Neurologic toxicity resolved in three patients before the onset of CRS. Eighteen patients experienced neurologic toxicity after resolution of CRS.

The most common neurologic toxicities included encephalopathy (24%), tremor (14%), aphasia (9%), delirium (7%), headache (7%), dizziness (6%), and ataxia (6%). Serious events including cerebral edema and seizures occurred with BREYANZI. Fatal and serious cases of leukoencephalopathy, some attributable to fludarabine, have occurred in patients treated with BREYANZI.

CRS and Neurologic Toxicities Monitoring

Monitor patients daily at a certified healthcare facility during the first week following infusion, for signs and symptoms of CRS and neurologic toxicities. Monitor patients for signs and symptoms of CRS and neurologic toxicities for at least 4 weeks after infusion; evaluate and treat promptly. Counsel patients to seek immediate medical attention should signs or symptoms of CRS or neurologic toxicity occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

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.BreyanziREMS.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. Infections (all grades) occurred in 45% (121/268) of patients. Grade 3 or higher infections occurred in 19% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections occurred in 5%, and viral and fungal infections occurred in 1.5% and 0.4% of patients, respectively. Monitor patients for signs and symptoms of infection before and after BREYANZI administration and treat appropriately. Administer prophylactic antimicrobials according to standard institutional guidelines.

Febrile neutropenia has been observed in 9% (24/268) of patients after BREYANZI infusion and 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.

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. Ten of the 11 patients in the TRANSCEND study with a prior history of HBV were treated with concurrent antiviral suppressive therapy to prevent HBV reactivation during and after treatment with BREYANZI. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

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 31% (84/268) of patients, and included thrombocytopenia (26%), neutropenia (14%), and anemia (3%). Monitor complete blood counts prior to and after BREYANZI administration.

Hypogammaglobulinemia

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with BREYANZI. The adverse event of hypogammaglobulinemia was reported as an adverse reaction in 14% (37/268) of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 21% (56/268) of patients. Hypogammaglobulinemia, either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion, was reported in 32% (85/268) 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 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, during this initial period.

Adverse Reactions

Serious adverse reactions occurred in 46% of patients. The most common nonlaboratory, serious adverse reactions (> 2%) were CRS, encephalopathy, sepsis, febrile neutropenia, aphasia, pneumonia, fever, hypotension, dizziness, and delirium. Fatal adverse reactions occurred in 4% of patients.

The most common nonlaboratory adverse reactions of any grade ($\geq 20\%$) were fatigue, CRS, musculoskeletal pain, nausea, headache, encephalopathy, infections (pathogen unspecified), decreased appetite, diarrhea, hypotension, tachycardia, dizziness, cough, constipation, abdominal pain, vomiting, and edema.

Please see full [Prescribing Information](#), including **Boxed WARNINGS** and [Medication Guide](#).

Bristol Myers Squibb: Creating a Better Future for People with Cancer

Bristol Myers Squibb is inspired by a single vision—transforming patients' lives through science. The goal of the company's cancer research is to deliver medicines that offer each patient a better, healthier life and to make cure a possibility. Building on a legacy across a broad range of cancers that have changed survival expectations

for many, Bristol Myers Squibb researchers are exploring new frontiers in personalized medicine, and through innovative digital platforms, are turning data into insights that sharpen their focus. Deep scientific expertise, cutting-edge capabilities and discovery platforms enable the company to look at cancer from every angle. Cancer can have a relentless grasp on many parts of a patient's life, and Bristol Myers Squibb is committed to taking actions to address all aspects of care, from diagnosis to survivorship. Because as a leader in cancer care, Bristol Myers Squibb is working to empower all people with cancer to have a better future.

About Bristol Myers Squibb

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at BMS.com or follow us on [LinkedIn](#), [Twitter](#), [YouTube](#), [Facebook](#) and [Instagram](#).

Juno Therapeutics, Inc. is a wholly owned subsidiary of Bristol-Myers Squibb Company. The approval of *Breyanzi* is based on a Biologics License Application that was submitted by Juno Therapeutics. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol Myers Squibb company and Juno Therapeutics, a Bristol Myers Squibb company.

Bristol Myers Squibb Cautionary Statement Regarding Forward-Looking Statements

This press release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, whether Breyanzi for the indication described in this release will be commercially successful and that continued approval of such product candidate for such indication described in this release may be contingent upon verification and

description of clinical benefit in confirmatory trials. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb's business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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