Dr. Gordon was contracted with Bristol Myers Squibb for this article but did not receive any compensation for sharing his perspective for this story

Chimeric antigen receptor (CAR) T cell therapy is a personalized approach to treating certain blood cancers and is one of the most impactful advances in immunotherapy care seen in the last 20 years. CAR T cell therapy works by leveraging the immune system's inherent ability to fight cancer, genetically engineering a patient's own T cells to recognize and bind to proteins found on the surface of certain cancer cells. This interaction leads to the activation of the CAR T cells, which can then kill their target cells and continue to multiply within the body.[1–4]

There are currently six U.S. Food and Drug Administration (FDA) approved CAR T cell therapies, each targeting B-cell markers CD19 or BCMA and indicated to treat select blood cancers. Investigational CAR Ts that recognize new targets and multiple antigens at once are also being developed to help expand cell therapy beyond blood cancers.[5]

Leo Gordon, MD, is a professor of medicine in hematology and oncology at Northwestern University Feinberg School of Medicine and the Robert H. Lurie Comprehensive Cancer Center. He has seen the clinical development of CAR T treatments as a result of clinical research and is a passionate advocate for making cell therapies available for appropriate patients.

"Between my research and clinical activities, I have witnessed first-hand what CAR T cell therapies are capable of delivering, especially for patients that have run out of viable treatment options," said Dr. Gordon. "Lymphoma, in particular, is an area where CAR T cell therapies have resulted in significant responses and long remissions, improving outcomes for patients who had limited options just five years ago."

The promise and future of cell therapy in treating relapsed or refractory LBCL

Large B-cell lymphoma (LBCL) is a form of non-Hodgkin's lymphoma that comprises about 30% of all non-Hodgkin's lymphoma cases and is diagnosed in approximately 150,000 people worldwide annually.[6] Roughly 60% of patients with LBCL achieve long-term remission with initial chemoimmunotherapy, leaving as many as 40% that do not respond or relapse after treatment.[7]

Typical second-line treatments, including high-dose chemotherapy and stem-cell transplantation, can improve outcomes; however, patients who are resistant to initial treatment or relapse early often fail to achieve long-term benefits.[8] Therefore, personalized therapy options have been approved for patients with relapsed or refractory (R/R) LBCL.[9]

CD19 is a critical target as it is broadly expressed among many B-cell malignancies, including LBCL. With CD19-targeting CAR T cell therapies, T cells are genetically reprogrammed to help recognize and target CD19-expressing cells, which may include healthy and cancerous cells.[10]

"The availability of a CAR T cell therapy as a second-line treatment is crucial, as some types of large B-cell lymphoma quickly worsen, and patients can't afford to wait before finding a promising option," said Dr. Gordon. "CAR T cell therapy is a personalized treatment for patients with certain relapsed or refractory blood cancers. Fortunately, CAR T cell therapies are available for relapsed or refractory large B-cell lymphoma patients earlier in the treatment journey, like *Breyanzi*® (lisocabtagene maraleucel)."[11]

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with 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. BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.

Please see the Important Safety Information below on serious side effects including Boxed WARNINGS for cytokine release syndrome (CRS) and neurologic toxicities (NT).

Serious side effects such as CRS, NT, hypersensitivity reactions, severe infections, including life-threatening or fatal infections, prolonged cytopenias, hypogammaglobulinemia, secondary malignancies and effects on the ability to drive and use machines may occur with *Breyanzi*. Other common side effects of *Breyanzi* include fever, fatigue, musculoskeletal pain, and nausea.

Like many other CAR T cell therapies, *Breyanzi* was first approved for use later in a patient's treatment journey, after two or more lines of systemic therapy. A few years later, the FDA approved it as a second-line treatment based on results from the TRANSFORM and PILOT clinical trials.[11]

TRANSFORM is a pivotal, global, randomized, open-label multicenter Phase 3 trial evaluating *Breyanzi* compared to current standard therapy regimens (platinum-based

salvage chemotherapy followed by high-dose chemotherapy and autologous HSCT in patients responding to salvage chemotherapy) in adult patients with LBCL that was primary refractory or relapsed within 12 months after first-line chemoimmunotherapy.

In the TRANSFORM study (n=184), at interim analysis after a median follow-up of 6.2 months, median event-free survival (mEFS) was 10.1 months for *Breyanzi* vs 2.3 months for standard therapy, a 4x improvement.[11,12] At this point in follow up, *Breyanzi* also demonstrated a 66% reduction in risk of EFS events.[11] In the primary analysis with a median follow-up of 17.5 months, mEFS was not reached in patients who received *Breyanzi* vs 2.4 months for standard therapy. With *Breyanzi*, the majority (73.9%) of patients achieved a complete response (CR) compared to less than half (43.5%) of those who were treated with standard therapy.[13]

PILOT is a multicenter Phase 2 single-arm, open-label trial evaluating *Breyanzi* as a second-line therapy in adults with R/R LBCL after first-line therapy who are ineligible for HSCT. In a median follow up at 11.2 months for the Phase 2 PILOT study (n=61), 80% (49/61) of patients achieved the primary endpoint of overall response rate (ORR) and over half (54%; 33/61) of the patients showed a CR to *Breyanzi*.[12]

"By recognizing the advantages of using CAR T cell therapy treatments earlier, we can give patients an option to treat their large B-cell lymphoma," said Dr. Gordon, a PILOT and TRANSCEND study investigator. "*Breyanzi* offers significantly improved clinical outcomes and an established safety profile, demonstrating clinically meaningful complete responses, event-free survival, and progression-free survival compared to standard therapy (stem cell transplant) in patients with relapsed or refractory large B-cell lymphoma that are primary refractory or relapsed within 12 months after first-line therapy. These points are also evident for patients who have relapsed after primary treatment but who are not good candidates for stem cell transplant as demonstrated in the non-randomized PILOT study."

Patients with R/R LBCL, which is typically diagnosed in elderly adults over 60 years of age, are more likely to have comorbidities that can limit their therapeutic options. So, while the recommended frontline therapies for LBCL can be effective for many patients, they often involve chemotherapeutic agents, which may not be appropriate for older patients or those who have undergone multiple treatment rounds.[14]

Regarding this vulnerable LBCL patient population, Dr. Gordon adds, "If the first-line treatment fails, these patients may be unsure of their next steps, so it is important to address their concerns and provide them with the most appropriate options earlier in their treatment plan."

"For physicians looking to guide their patients as they embark on their CAR T cell treatment journey, I would advise them to emphasize that CAR T cell therapy can be effective with a one-time infusion treatment which includes leukapheresis, manufacturing, administration, and adverse event monitoring," said Dr. Gordon. "The possibility of serious side effects such as cytokine release syndrome or neurological toxicities is real and must be monitored.[11,12,15] It is important to help patients weigh the potential risks against the potential benefits."

All patients are monitored closely by their care team for four weeks for possible side effects, which may be severe, life-threatening or even fatal. These side effects can include but are not limited to CRS and NT, which can happen in the first few days to several weeks after a patient's CAR T cells are infused into their body. Time at the treatment center and follow-up visits will vary based on the individual patient.

Breyanzi has a well-established safety profile based on results from the TRANSFORM and PILOT studies. Occurrences of CRS and neurologic events were generally low grade and mostly resolved quickly with standard protocols, and without the use of prophylactic steroids. Any-grade CRS was reported in less than half of patients (45%; 68/150), with Grade 3 CRS reported in 1.3% of patients. Any-grade neurologic events were reported in 27% (41/150) of patients treated with *Breyanzi*, with Grade 3 neurologic events reported in 7% of patients. Median time to onset of CRS was four days (range: 1 to 63 days) and median duration of CRS was four days (range: 1 to 16 days). The median time to onset of neurologic events was eight days (range: 1 to 63 days). The median duration of neurologic toxicities was six days (range: 1 to 119 days). [11]

Adding CAR T cell therapy to the list of approved and available second-line treatments for LBCL expands much-needed treatment options for high-risk patients earlier.

"Innovations in personalized cancer care, like CAR T therapies, are evolving rapidly, but these therapies can only be as transformative as their implementation allows, and physicians play an essential role in these efforts," said Dr. Gordon. "Identifying the appropriate therapy and incorporating it into the patient's treatment plan as early as they are eligible is a way to help realize the potential of these CAR T therapies."

To learn more about *Breyanzi*, please visit https://www.breyanzihcp.com/.

Important Safety Information and Indication

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)

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with BREYANZI. Among patients receiving BREYANZI for LBCL (N=418), CRS occurred in 46% (190/418), 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).

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.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.

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.

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.

Please see full Prescribing Information, including Boxed WARNINGS and Medication Guide.

Indication

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.

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

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