CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Approval of Lisocabtagene Maraleucel in Chronic Lymphocytic Leukemia

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H&O When did lisocabtagene maraleucel first receive approval?

WW The US Food and Drug Administration (FDA) first approved lisocabtagene maraleucel (liso-cel; Breyanzi, Bristol Myers Squibb) on February 5, 2021. This approval, based on the TRANSCEND NHL 001 trial, was for the treatment of relapsed or refractory (R/R) large B-cell lymphoma after 2 or more lines of systemic therapy.[1] The FDA subsequently approved liso-cel on June 24, 2022, for the treatment of adults with R/R large B-cell lymphoma after 1 prior line of systemic therapy; this approval was based on the TRANSFORM trial.[2] Most recently, on March 14 of this year, liso-cel received accelerated approval for use in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) after at least 2 prior treatments, including a BTK inhibitor and a BCL2 inhibitor; approval was based on the results of the TRANSCEND CLL 004 trial.[3]

H&O How important is the approval of this new indication in CLL?

WW The new indication is important for several reasons. First, liso-cel is the first chimeric antigen receptor (CAR) T-cell product to be approved for patients with CLL, and I believe it will be the only CD19-directed T-cell product approved to treat patients with CLL for the foreseeable future. Second, approval for this indication provides a treatment option for those patients who have an unmet medical need. We have been very successful in developing targeted small-molecule inhibitor–based therapy for patients who have CLL, but we still see resistance to both Bruton tyrosine kinase (BTK) inhibition and BCL2 inhibition. Pirtobrutinib (Jaypirca, Lilly), an oral, noncovalent, reversible BTK inhibitor, was approved for this population of patients on December 1, 2023. The phase 1/2 BRUIN trial found an overall response rate of 72% and a median progression-free survival of 12.2 months with pirtobrutinib in these patients (NCT03740529). Liso-cel is now also available for this population of patients with CLL, who have a short expected survival.

H&O Could you discuss the research that led to the approval for this new indication?

WW TRANSCEND CLL 004 was a phase 1b/2 trial that evaluated 2 dose levels of liso-cel in previously treated patients with CLL. The study included a subgroup of patients who had received at least 2 prior treatments, including a BTK inhibitor and a BCL2 inhibitor. In this subgroup, the complete remission rate was 20% and the overall response rate was 45%. The responses were durable, with a median progression-free survival of 12 months overall and 26 months among the 25% of patients who achieved a partial remission. Progression developed in just one patient who had achieved a complete remission, so those patients who achieved remission did exceptionally well. The data on this subgroup served as the basis for the accelerated approval of liso-cel in CLL/SLL.

H&O What are the adverse events associated with liso-cel?

WW The adverse events that we are most concerned about with CAR T-cell therapy are cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). CRS occurs when the CAR T cells become activated in the patient, expand, and produce cytokines that lead to fevers, hypotension, chills, tachycardia, and headache, much like the symptoms of a severe viral infection. CRS can also lead to hypoxemia and hypotension; in some cases, patients require intravenous fluids. In TRANSCEND CLL 004, 83% of patients experienced any-grade CRS, but only 9% of them experienced grade 3 or higher CRS. CRS was managed with corticosteroids and/or tocilizumab, an anti–interleukin 6 compound. We also use agents such as acetaminophen to address fevers and headaches. The development of CRS is a good sign because it means that the treatment is working. We just want the CRS to be manageable, which it was for patients in this study. But even the patients in whom CRS does not develop are able to respond to CAR T-cell therapy.

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ICANS can be associated with headache, confusion, tremor, and sometimes delirium and seizure. In TRANSCEND CLL 004, 46% of patients experienced any-grade ICANS, and 20% of patients experienced grade 3 or higher ICANS. All these cases were effectively managed with corticosteroids. As with CRS, acetaminophen can be used as needed for symptoms.

H&O How common is the use of liso-cel for CLL at this point?

WW The commercial use of liso-cel in CLL is not yet common because it was just approved for this indication, but the numbers will certainly increase with time. We have used liso-cel in many patients with CLL at MD Anderson through the clinical trial, however.

H&O Are you seeing any barriers to use?

WW Reimbursement should not a problem now that the treatment has FDA approval and is part of the National Comprehensive Cancer Network guidelines.[4] Patients must meet the criteria, of course, and the procedure requires insurance preapproval. One barrier to liso-cel access may be that it has to be given at a center of excellence with experience in the procedure and in managing CRS and ICANS. Patients who are receiving care at a community practice must be referred to a center of excellence to receive liso-cel. The treatment can be given on an outpatient basis, but patients have to remain close to the center for monitoring during the first 4 weeks after administration, a requirement that can impose logistic challenges.

H&O What ongoing studies are looking at liso-cel for CLL or related conditions?

WW We just reopened the TRANSCEND CLL 004 trial because the FDA, as one of the conditions for accelerated approval, requested data on 50 additional patients who had previously received both BTK and BCL2 inhibitors for CLL. CD19-directed T-cell therapy has the potential to be used in any CD19-positive B-cell malignancy, including mantle cell lymphoma. CAR T-cell therapy directed against other surface proteins is even being examined for use in solid tumors, including glioblastoma (NCT05768880).

H&O What future studies would you like to see?

WW I would like to see research looking at the use of liso-cel in earlier lines of treatment, particularly in very high-risk populations of patients, such as those with a 17p deletion or mutated *TP53*. We know from single-center studies that some patients who receive CD19-directed CAR T-cell therapy can have long remissions and may be cured of their disease. It would be great to see if we could achieve long-term remissions in patients who are expected to have short remissions with our current standard-of-care first-line treatments.

Another area of interest is studying the activity of liso-cel in combination with other agents, such as BTK inhibitors. The TRANSCEND CLL 004 trial included 3 arms: 1 for liso-cel as monotherapy, 1 for liso-cel combined with BTK inhibition, and 1 for liso-cel plus venetoclax (Venclexta, AbbVie). Data from Fraietta and colleagues showed that the administration of a BTK inhibitor such as ibrutinib (Imbruvica, Pharmacyclics/Janssen) for a few

cycles before T-cell collection improved the quality of the CAR T-cell product, creating a more potent product.[5] I would like to see studies that look at a combination of lisocel and the newer BTK inhibitors, such as pirtobrutinib, in patients with CLL or Richter transformation.

Disclosures

Dr Wierda has conducted contracted research for AbbVie, Acerta Pharma/AstraZeneca Group, Bristol Myers Squibb, Cyclacel Pharmaceuticals, Genentech/Roche Group, Gilead Sciences, GlaxoSmithKline, Janssen Biotech, Juno Therapeutics/Celgene, Kite/Gilead, Loxo Oncology/Lilly, Novartis, Oncternal Therapeutics, Pharmacyclics/AbbVie, Nurix Therapeutics, Numab Therapeutics, and BeiGene. He is the chair of CLL for the National Comprehensive Cancer Network, is supported by the NIH/NCI under award number P30 CA016672, and has used MDACC Cancer Center Support Grant (CCSG) shared resources.

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