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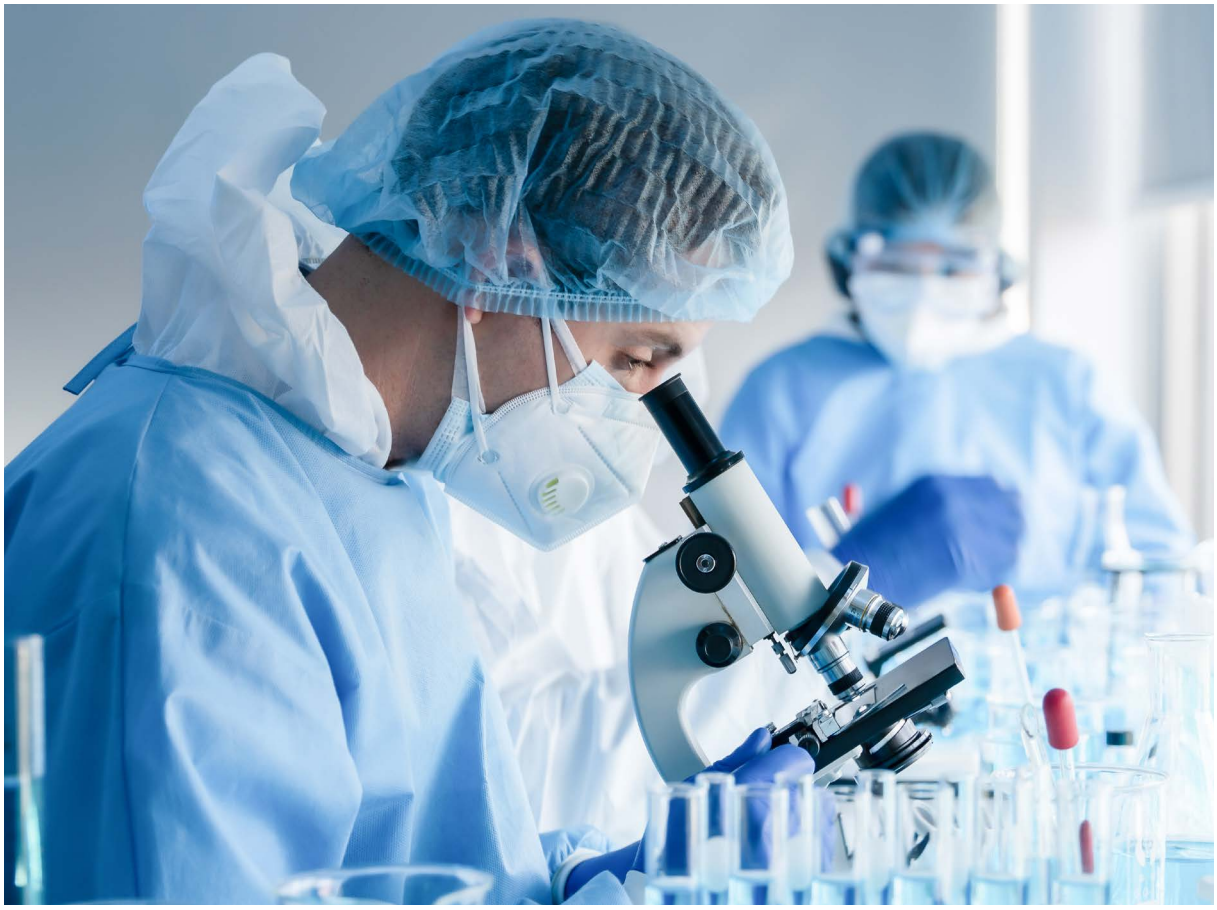
NEWSLETTER



Clinician Update: Leukemia

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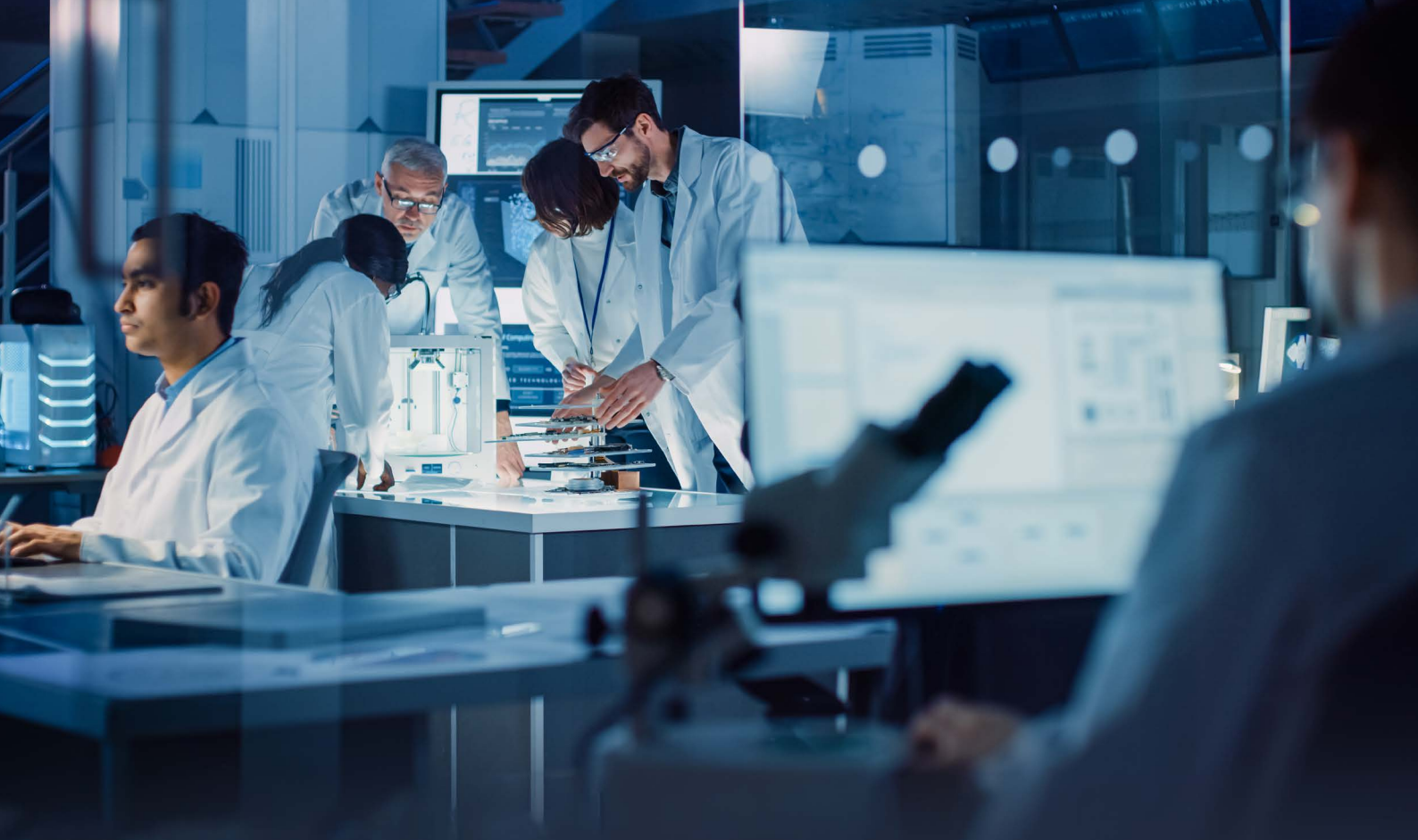


What's New in CAR T-Cell Therapy?

CAR T-cell therapy has revolutionized the management of advanced leukemia and other blood cancers, but investigators continue to learn more about these innovative treatments.

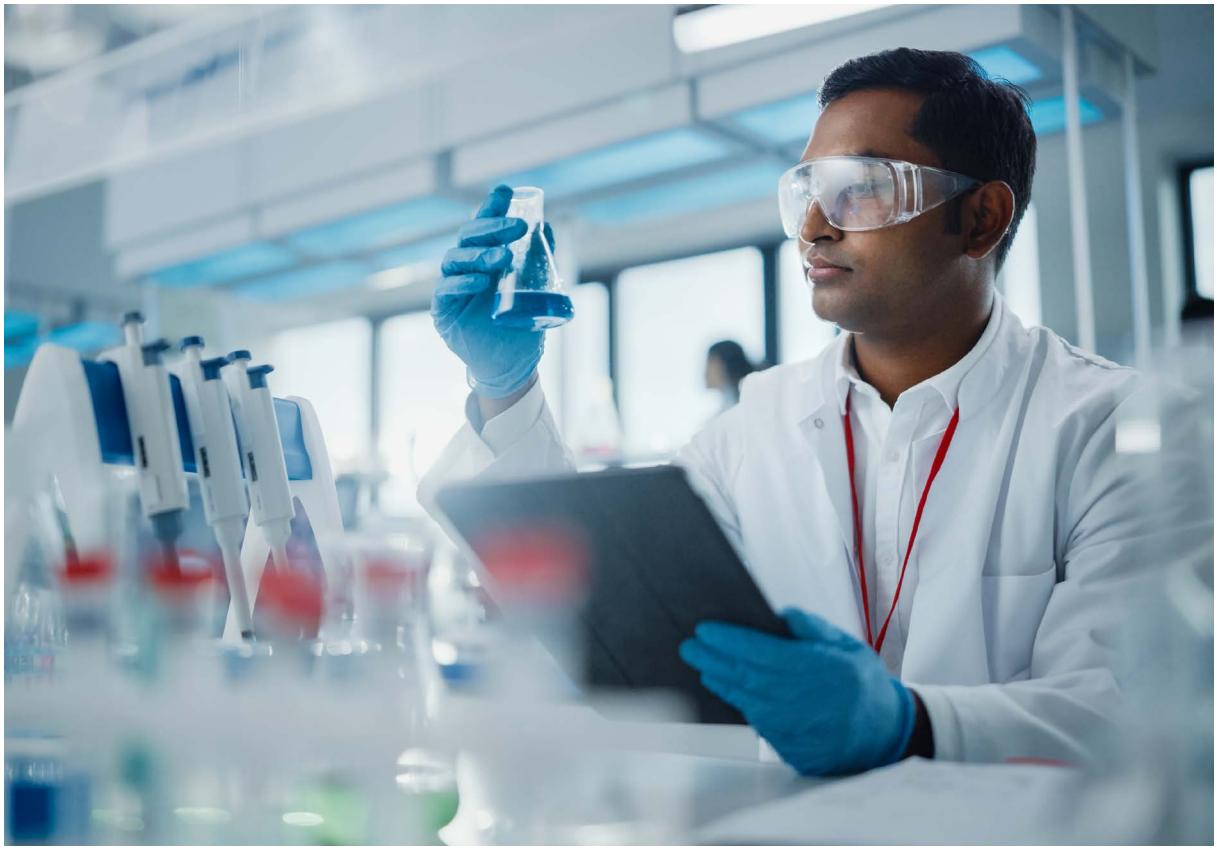
The management of leukemia and other hematologic malignancies entered a new era in 2017, when the U.S. Food and Drug Administration approved tisagenlecleucel (Kymriah), the first chimeric antigen receptor (CAR) T-cell therapy to reach the market. Today, there are a half dozen forms of CAR T-cell therapy used to treat various forms of blood cancer. CAR T-cell therapy offers hope to patients with refractory or relapsed leukemias, most of whom in earlier days would have had few options beyond palliative care. Yet, while CAR T-cell therapy has become well entrenched in the treatment of leukemia, lymphoma, and other blood cancers, investigators continue to learn more about its potential. Here are three recent developments.

Long-Term Persistence of CAR T-Cell Therapy Reported in CLL

Early in 2022, researchers at the Abramson Cancer Center and the Perelman School of Medicine at the University of Pennsylvania reported in *Nature* that two patients with end-stage chronic lymphocytic leukemia (CLL) who received then-experimental CAR T-cell therapy in 2010 remained in remission and cancer free for over a decade. That represents the longest recorded remission for CLL following CAR T-cell therapy. Tests showed that CAR T cells remained detectable and active, with long-term remission apparently controlled by CD4+ T cells. While one of the patients died of complications related to COVID-19 infection in 2021, the other is a dedicated long-distance runner who has competed in six half marathons, and serves as a fundraiser for the Leukemia & Lymphoma Society (see page 8).

CAR T-cell dosing: Is higher better?

Administering tisagenlecleucel (Kymriah) at the higher end of the approved dosing range led to improved responses without increasing side effects in pediatric patients with B-cell acute



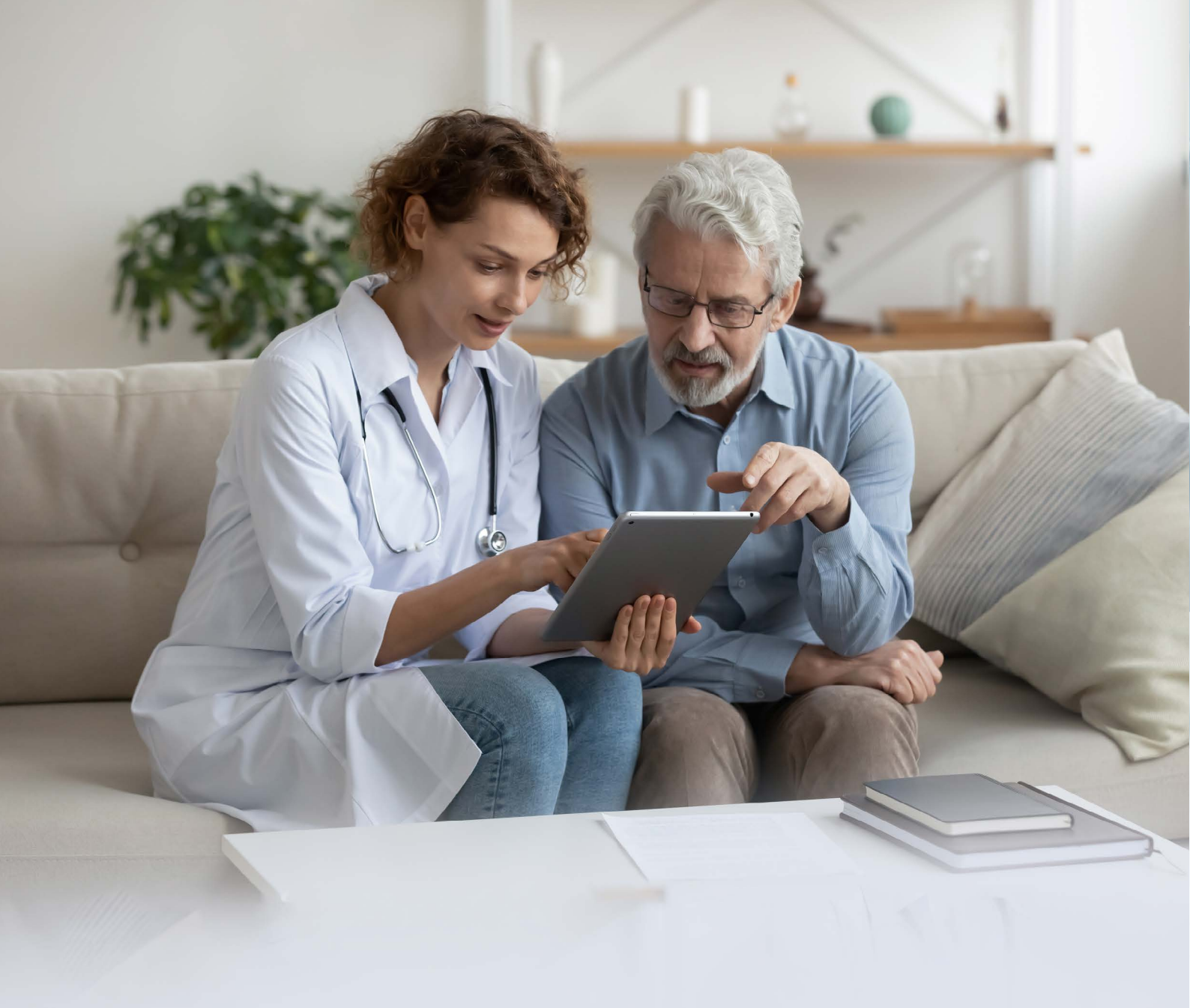
lymphoblastic leukemia (ALL), according to a study published last August in *Blood Advances*. Tisagenlecleucel is approved for patients up to 25 years of age with B-cell ALL that is refractory or relapsed. While this form of CAR T-cell therapy offers an important new option for this patient population, its wide dosing range often left clinicians unsure whether using higher doses would risk toxicity.

In the *Blood Advances* study, a team led by pediatric oncologist Liora Schultz, MD, of the Stanford Children's Health–Lucile Packard Children's Hospital compared overall, event-free, and relapse-free survival among young patients with refractory or relapsed B-cell ALL treated with varying doses of tisagenlecleucel. At one year, patients given the higher doses (between 2.4 and 5.1 million cells/kg) had significantly higher rates of survival by all means measured than those treated with lower doses. Among patients treated with the highest dose, 86 percent were alive, compared to 59 percent in the lowest-dose group. Adverse effects did not appear to be increased in patients receiving higher doses.

'Off the shelf' CAR T-cell therapy continues to emerge

While CAR T-cell therapy has revolutionized the treatment of leukemia and other blood cancers, it's time consuming, complex, expensive, and has other downsides that may make it less accessible for some patients. Allogeneic CAR T cells from healthy donors could minimize many of those problems and create new possibilities, such as combining cells directed against different targets. However, "off the shelf" T cells have their own potential concerns, such as graft-versus-host (GVH) disease.

Using CRISPR technology and other gene-engineering methods, researchers have developed allogeneic CAR T cells that overcome the threat of GVH disease and are undergoing evaluation in clinical trials. Last December, a team from University College London and Great Ormond Street Hospital for Children announced the first use of a new CRISPR technique called base-editing to modify allogenic cells for CAR T-cell therapy. The recipient was the first patient enrolled in the TvT CAR7, a phase 1 trial of off-the-shelf CAR



T-cell therapy, a teen named Alyssa with T-cell acute lymphoblastic leukemia that had failed to respond to other treatments. Within a month she was in remission. After receiving a bone-marrow transplant to restore her immune system, Alyssa remained cancer free for six months, when these preliminary findings were reported.

At the American Society of Hematology meeting last December, Fate Therapeutics presented interim data from its ongoing trial of an investigational allogeneic CAR T-cell treatment called FT819 in patients with relapsed or refractory B-cell lymphoma. FT819, which is derived from an induced pluripotent stem cell (iPSC) line, is engineered to disrupt T-cell receptor expression, which eliminates the problem of GVH disease, among other enhancements that increase its efficacy and tolerability. In this phase 1 trial, one of two patients naïve to CAR T-cell therapy, who had diffuse large B-cell lymphoma (DLBCL) and was previously treated with five lines of therapy, had a complete response. Among patients previously treated with CAR T-cell therapy, two of six patients achieved an objective response, including one complete response in a patient with DLBCL previously treated with seven lines of therapy who did not respond to autologous CAR T-cell therapy.

Other clinical trials of off-the-shelf immunotherapy are underway. For example, researchers at the University of Toronto and the First Affiliated Hospital of University of Science and Technology of China are conducting trials of "double negative" T cells (which are engineered to lack CD4 and CD8 receptors found on normal T cells) in patients with high-risk acute myeloid leukemia.

Research News

Second-Generation BTK Inhibitor has Greater Efficacy, Fewer Adverse Effects in CLL

The second-generation Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib (Brukinsa) had superior progression-free survival and less cardiac toxicity than ibrutinib (Imbruvica) in a phase 3 trial that included patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Ibrutinib, a first-generation BTK inhibitor, has become a standard-care therapy for CLL, as first-line treatment and for relapsed or refractory disease. However, increased risks of atrial fibrillation, hypertension, and other cardiac events limit the use of ibrutinib. Zanubrutinib was designed to be more specific and to have more sustained binding to BTK than its predecessor.

In this multinational study, 652 patients were randomly chosen to receive zanubrutinib or ibrutinib. At two years, progression-free survival was 78.4 percent in the zanubrutinib group, compared to 65.9 percent in the ibrutinib group. This advantage was significantly enhanced in patients with a 17p deletion, a TP53 mutation, or both. Adverse effects were lower in the zanubrutinib group, including a lower incidence of cardiac disorders (21.3 percent to 29.6 percent. One patient in the zanubrutinib group stopped treatment due to cardiac side effects, compared to 14 patients in the ibrutinib arm.

Triplet Therapy May Be an Option for High-Risk CLL

A combination of targeted therapies proved effective in treating high-risk CLL, according to

the results of a phase 2 trial reported at the 2022 American Society of Hematology (ASH) Annual Meeting and Exposition in New Orleans last December. High-risk CLL is characterized by clinical and/or genetic resistance to treatment with chemoimmunotherapy. In the trial, 68 patients with previously untreated CLL received a combination regimen of acalabrutinib (Calquence), venetoclax (Venclexta), and obinutuzumab (Gazyva) for up to 16 cycles. At a median follow-up of 35 months, 83 percent of the participants had undetectable minimal residual disease (MRD) in their bone marrow, and 45 percent of those patients had complete remission and undetectable MRD. Treatment was well tolerated. In an earlier group of that included all CLL patients, this triplet therapy achieved deep remission in 89 percent of participants, according to *The ASCO Post*.

Immediate Progression to Stem Cell Transplant May Benefit Refractory/Relapsed AML

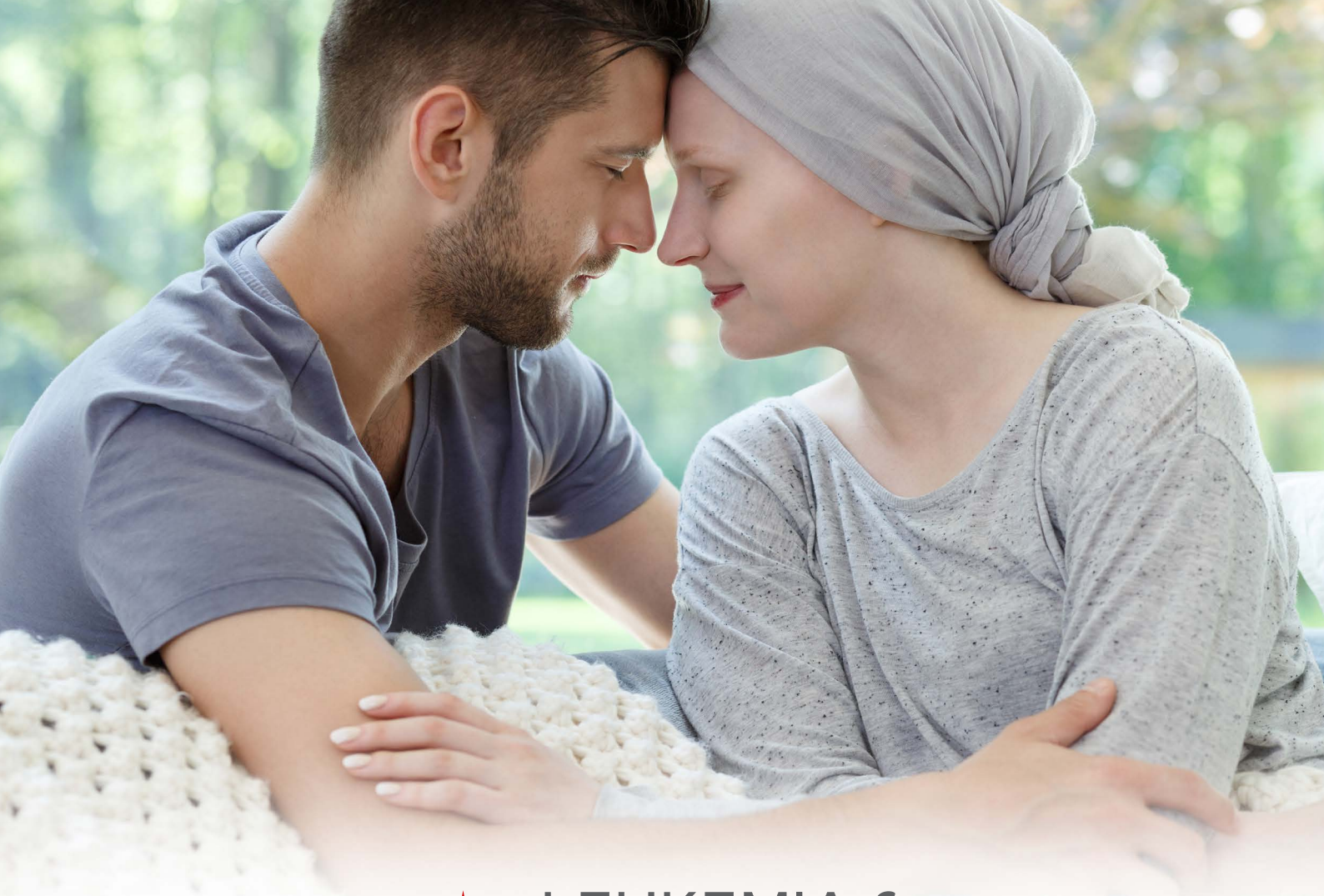
In another study presented at ASH, German researchers challenged practice orthodoxy of only offering stem cell transplantation (STC) to leukemia patients who are in complete remission. In the first phase 3 trial of its kind, investigators recruited 281 patients with acute myeloid leukemia (AML) that had relapsed or failed to respond to chemotherapy to participate. Half underwent intensive salvage chemotherapy with the goal of achieving remission prior to receiv-

ing STC, while the other half proceeded directly to transplantation. At day 56 following transplant, 84.1 percent of patients in the direct-to-SCT arm achieved remission, compared to 81.3 percent of patients in the salvage chemotherapy arm. Overall survival at one year and three years (roughly 70 percent and 50 percent, respectively) was similar in both groups. Authors of the study suggest that these findings indicate that refractory/relapsed AML patients can skip salvage chemotherapy, which would reduce time in hospital, cost, and toxicity.

FDA Approves Olutasidenib for Relapsed or Refractory AML

In December, the FDA approved the IDH1 inhibitor olutasidenib (Rezlidhia) for relapsed or refractory acute myeloid leukemia (AML). The IDH1 gene encodes the enzyme IDH1, which cells need to produce energy from fats and guard against reactive oxygen species. Mutations in IDH1 are associated with certain cancers, including AML.

The FDA based its approval on an open-label, single-arm, multicenter clinical trial that included 147 adult patients with relapsed or refractory AML, who tested positive for the IDH1 mutation. confirmed using the above assay. Patients received olutasidenib (150 mg twice daily, orally) until disease progression or unacceptable toxicity, or until hematopoietic stem cell transplantation. Median treatment duration of 4.7 months. The rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh) was 35 percent (32 percent CR and 2.7 percent CRh). The most common adverse reactions were nausea, fatigue or malaise, arthralgia, constipation, leukocytosis, dyspnea, fever, rash, mucositis, diarrhea, and transaminitis. Olutasidenib has a Boxed Warning for the risk of differentiation syndrome.



LEUKEMIA & LYMPHOMA SOCIETY®

For Your Patients:

Where To Turn for Support

The Leukemia & Lymphoma Society

Patients with leukemia and other blood cancers can find support, information, and other resources at the Leukemia & Lymphoma Society (LLS). The LLS traces its roots to 1949, when New Yorkers Rudolph and Antoinette de Villiers, the parents of a teen who succumbed to leukemia five years earlier, established a fundraising and education organization in his name, known as the Robert Roesler de Villiers Foundation. The organization has changed names several times over the years, but has always been guided by the conviction that blood cancers are curable diseases. Today, LLS not only funds research on cures, but also provides a variety of services for patients, such as support groups and financial assistance. Learn more at lls.org.