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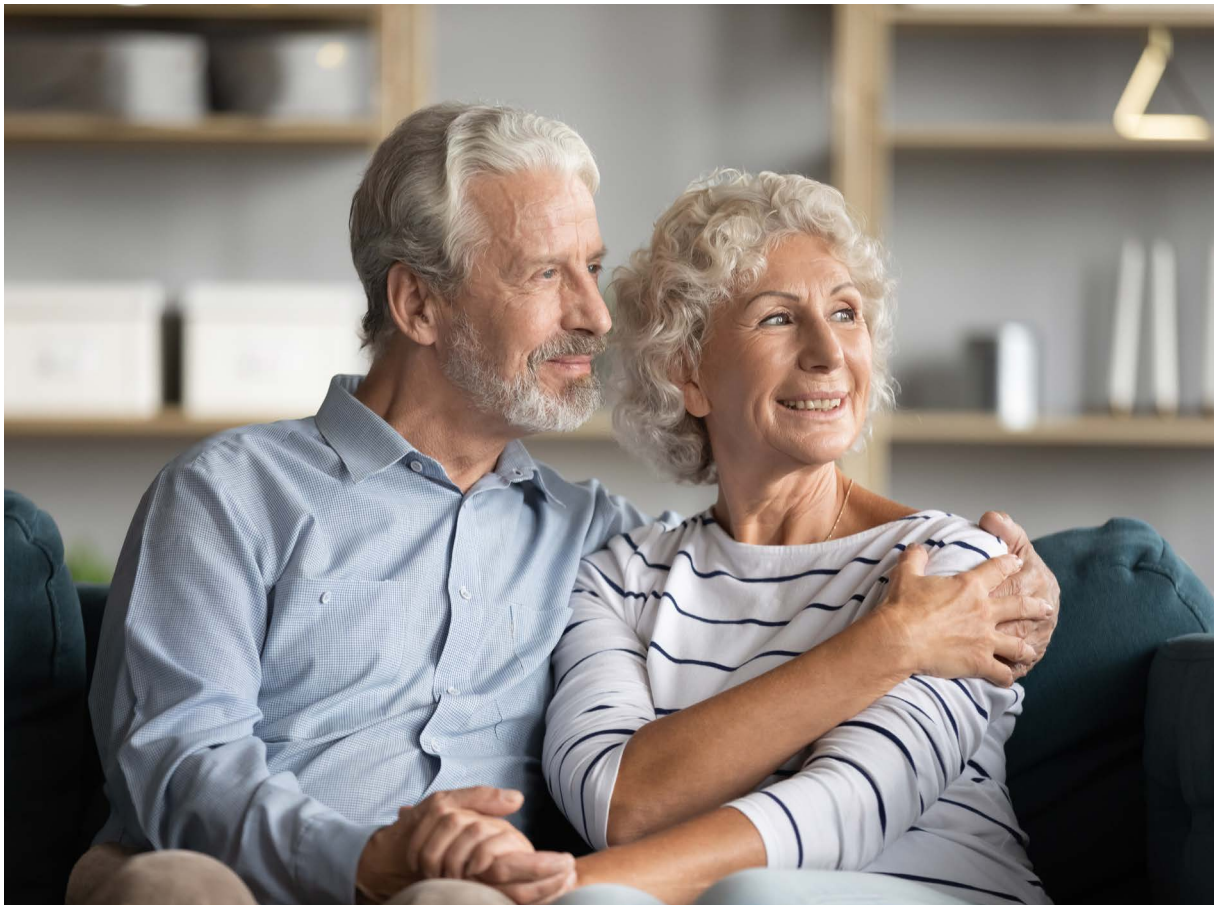
NEWSLETTER



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CAR T-Cell Therapy: New Hope for NHL

Treatment of non-Hodgkin lymphoma (NHL) poses a profound clinical challenge. While half of patients can be cured with modern frontline chemoimmunotherapy, outcomes for the remainder who relapse or are refractory to treatment tend to be poor. (With NHL typically diagnosed in older patients, stem cell transplantation is often not an option due to high toxicity.)

Yet, new hope for some NHL patients has arrived in the form of chimeric antigen receptor (CAR) T-cell therapy, notably for patients with relapsed or refractory (r/r) B cell malignancies. A recent review in *Biomedicines noted* the "[r]emarkable response rates and prolonged remissions" many of these patients have achieved thanks to CAR T-cell therapies.

CAR T-cell therapy is a form of immunotherapy that uses a patient's own immune cells to kill cancer cells. T cells are harvested from the patient and genetically modified to produce chimeric antigen receptors. The modified cells are grown in a lab, then infused back into the patient.

Four CAR T-cell therapies have been approved by the U.S. Food and Drug Administration (FDA). They include:

• Axicabtagene ciloleucel (*Yescarta*), for certain patients with r/r large B cell lymphoma (LBCL) and r/r follicular lymphoma (FL).

• Brexucabtagene autoleucel (*Tecartus*), for certain patients with r/r mantle cell lymphoma or r/r B-cell precursor acute lymphoblastic leukemia (ALL).

• Lisocabtagene maraleucel (*Breyanzi*), for a variety of patients with LBCL and certain patients with FL.

• Tisagenlecleucel (*Kymriah*), for certain pediatric and young adult patients with r/r B-cell ALL, r/r diffuse LBCL, and r/r FL.

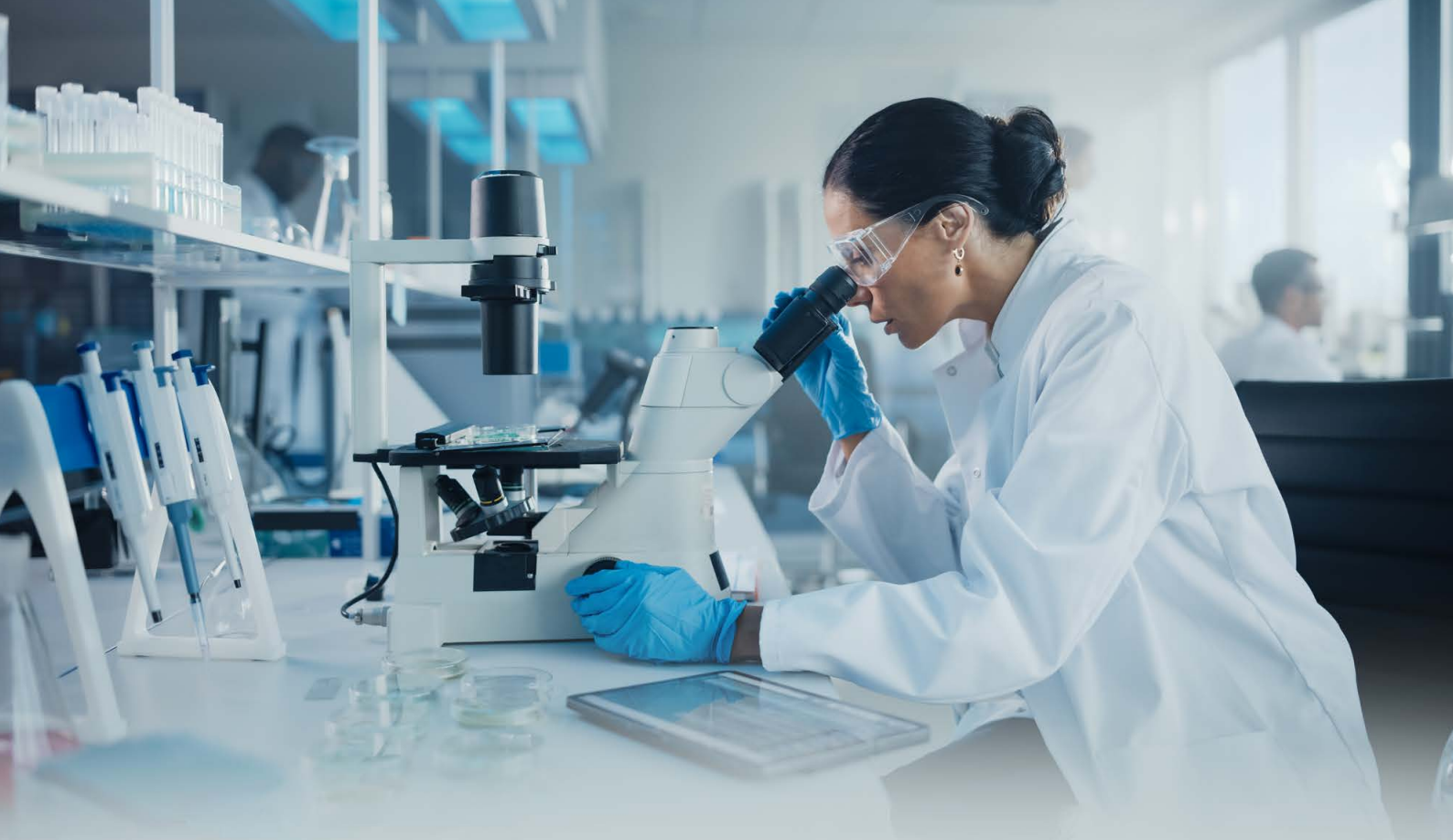
Initial approval of these drugs restricted their use to patients who had already failed multiple treatments, but there's growing momentum to deploy these therapies earlier. For instance, in July the FDA approved lisocabtagene maraleucel as a second-line therapy, meaning a patient must try only one other treatment (usually chemotherapy) before receiving CAR T cells. Axicabtagene ciloleucel was approved as a second-line treatment in April.

The next step in the development of these cutting-edge immunotherapies could be the emergence of allogenic CAR T-cells, which are produced from healthy donors and can be used "off the shelf," that is, with no need to harvest and modify the patient's T cells. In June, the FDA granted Regenerative Medicine Advanced Therapy (RMAT) designation to ALLO-501A (Allogene Therapeutics) in r/r LBCL. The RMAT designation was created through the 21st Century

Cures Act to expedite the development and review processes for promising pipeline products.

CAR T-cell therapy is associated with certain toxicities. The most common is cytokine-release syndrome (CRS), a supraphysiologic inflammatory state triggered by inflammatory cytokines and chemokines (such as interferon and tumor necrosis factor) released by CAR T-cells after they strike their target, antigen CD19. Symptoms can be managed with antipyretics and intravenous fluids for low-grade CRS, as well as anti-cytokine therapy and corticosteroids. Neurotoxicity is another possible side effect, though it tends to be self-limiting and reversible.

The success of CAR T-cell therapy has led to significant interest in developing additional agents; a recent count on clinicaltrials.gov found 686 clinical trials of CAR T-cell therapy for patients with lymphoma, other blood cancers, and solid tumors that are in preparation or currently recruiting. What's more, other new therapies for NHL and Hodgkin lymphoma are in development, too, including research studies underway by our pharma partners. Contact Massive Bio at (844) 627 7246 or support@massivebio.com to learn more and find out if your patients might be candidates for clinical trials.



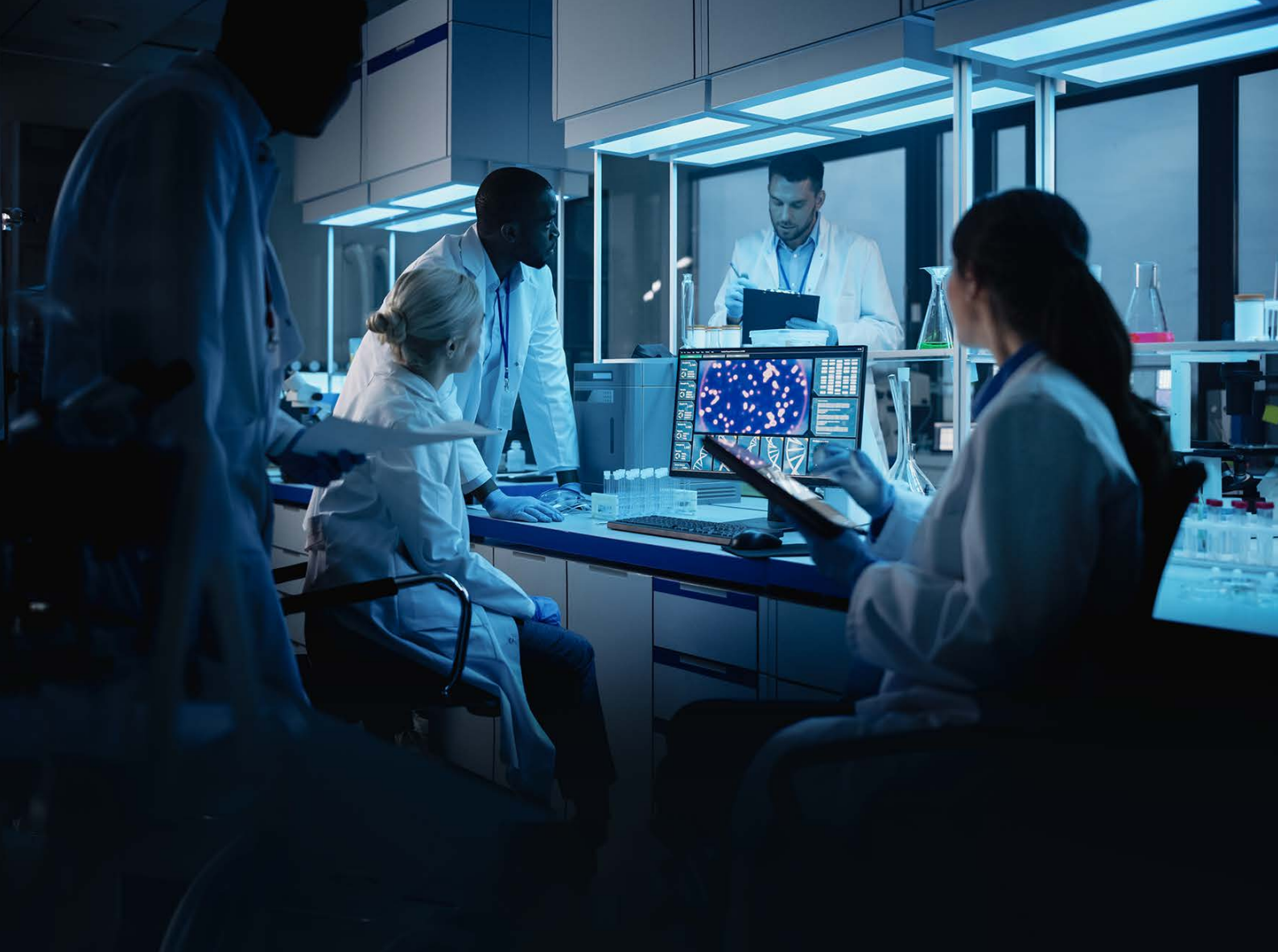
Clinical Trial News

First-Line Brentuximab Vedotin Improves Progression-Free Survival in Advanced Hodgkin Lymphoma

Adding brentuximab vedotin (*Adcetris*) to chemotherapy improves progression-free survival in patients with advanced Hodgkin lymphoma, according to newly reported six-year data from the ECHELON-1 study published in the *New England Journal of Medicine* in July. Brentuximab vedotin is a CD30-directed antibody-drug conjugate. (CD30 a transmembrane protein of the tumor necrosis factor family and a known tumor marker found on many kinds of lymphoma.)

In the trial, 664 patients with previously untreated stage III or IV classic Hodgkin lymphoma were assigned to receive brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD), while 670 similar patients received standard therapy of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Earlier, ECHELON-1 investigators reported superior progression-free survival at median follow-up of 24.6 months in the A+AVD group. Now, data from a median follow-up of six years are available.

The A+AVD combination continues to show superiority to standard therapy. At median follow-up of 73 months, 39 patients in the A+AVD group and 64 in the ABVD group had died (hazard ratio, 0.59). Six-year overall survival was estimated at 93.9% in the A+AVD group and 89.4% in the ABVD group. Progression-free survival was longer among recipients of A+AVD compared to patients in the ABVD arm, with a hazard ratio for disease progression or death of 0.68. Patients in the A+AVD arm also required less subsequent therapy, including transplantation, and had fewer second cancers (in 23 patients versus 32 patients). Peripheral neuropathy was more common with A+AVD than ABVD, but was resolved or ameliorated by the last follow-up. Authors of the study suggest that A+AVD should



be considered as the preferred first-line treatment for patients with previously untreated stage III or IV classical Hodgkin lymphoma.

Ibrutinib Plus Chemotherapy: New First-Line Option for Older MCL Patients

Mantle cell lymphoma (MCL) is often diagnosed in patients who are 65 or older, which means they usually are not candidates for intensive chemotherapy or stem cell transplantation, due to the high toxicity of these treatments. The results of the phase III SHINE trial, published in June in the *New England Journal of Medicine*, suggest that combining the BTK inhibitor ibrutinib (*Imbruvica*) with chemotherapy offers a much-needed new frontline option for this patient population. These findings were also reported at the American Society of Clinical Oncology Annual Meeting in June.

In the SHINE trial, 523 MCL patients 65 or older were randomized 1:1 to receive oral ibrutinib (560 milligrams once daily) until disease progression or unacceptable toxic effects or placebo. All patients received six cycles of bendamustine. If an objective response (complete or partial response) was achieved, patients were assigned to receive rituximab maintenance therapy, administered every eight weeks for up to 12 additional doses. The primary end point was progression-free survival.

At a median follow-up of 84.7 months, the median progression-free survival in the ibrutinib arm was 80.6 months compared to 52.9 months in the placebo group. Complete response in the ibrutinib group was 65.5% and 57.6% in the placebo group, though the difference was not statistically significant. Overall survival was similar in the two arms. Grade 3 or 4 adverse events were slightly more common in the ibrutinib group (81.5%) than in the placebo group (77.3%). The authors of this study have indicated that ibrutinib plus chemotherapy should become the new standard of care for older MCL patients.

For Your Patients: Where To Turn for Support **The Leukemia & Lymphoma Society**

Patients with myelofibrosis 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.