The work elegantly demonstrates how human iPSCs can be used to model the initiation of pediatric leukemia. By studying the ETO2::GLIS2 fusion in otherwise healthy cells, the onset of disease could be explored. Despite the challenges in generating transplantable iPS-derived hematopoietic cells, and the addition of only a single mutation, an engraftable leukemia was observed. Of clinical importance, the model may evolve into a drug screening platform for the development of novel treatment strategies.

*Conflict-of-interest disclosure: The authors declare no competing financial interests.* ■

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**IMMUNOBIOLOGY AND IMMUNOTHERAPY**

*Comment on Yu et al, page 1526*

# Prizloncabtagene autoleucel: a new CAR T cell for B-NHL

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**In this issue of *Blood*, Yu et al reported promising clinical results of prizloncabtagene autoleucel (prizlon-cel), a next-generation chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory B-cell non-Hodgkin lymphomas (r/r B-NHL).[1]**

The advent of anti-CD19 CAR T-cell therapy has revolutionized the treatment landscape for relapsed/refractory large B-cell lymphomas (r/r LBCL) and, in general, for r/r B-NHL. Long-term survival outcomes of 30% to 40% have been reported in pivotal clinical trials with tisagenlecleucel (tisa-cel), axicabtagene ciloleucel (axi-cel), lisocabtagene maraleucel (liso-cel) with these results confirmed in real-world settings.[2-5] These advances have enabled treatment for a patient population previously limited to palliative care. Unfortunately, the majority of patients who receive such therapies experience relapse or disease progression within the first 6 to 12 months after infusion. Anti-CD19 CAR T-cell failure is associated with a grim median survival of just 6 months.[6] Furthermore, few of these patients are eligible for additional treatments, with an even smaller subset able to undergo more advanced or intensive therapies, such as potentially curative allogeneic hematopoietic-cell transplantation. Therefore, it is of paramount importance to enhance the efficacy of CAR T-cell therapy. But what strategies have been employed to improve efficacy?

Two main approaches have been adopted. The first involves using CAR T-cell therapies earlier in the treatment sequence. For example, axi-cel and liso-cel have been tested as second-line treatments for high-risk LBCL in the ZUMA-7 and TRANSFORM trials, respectively.[7,8] Other trials are exploring the use of currently available anti-CD19 CAR T-cell therapies or newer cell therapies as first-line treatments. The second approach focuses on improving the efficacy of CAR T-cell therapy itself. Several methods have been investigated. One strategy is to reduce manufacturing time, addressing the fact that many patients progress before receiving CAR T-cell therapy. These efforts include testing in vivo CAR T-cell expansion and allogeneic "off-the-shelf" products. Another strategy involves modifying the CAR T-cell product, for example, using specific T-cell subpopulations (eg, adjusting the CD4:CD8 ratio) for manufacturing CAR T cells. Advances in transfection techniques, such as replacing lentiviral vectors with transposon- or CRISPR-based methods, have also been explored. Additionally, modifications to the CAR construct itself, either in its extracellular portion (eg, bispecific or bicistronic CARs) or its intracellular portion (eg, third- or fourth-generation CAR T cells), are being tested. A third approach involves combining CAR T-cell therapy with synergistic drugs, such as ibrutinib.

The results of the phase 1 trial of prizlon-cel, a bispecific CAR T-cell therapy targeting both CD19 and CD20, conducted by Yu and colleagues, represent a promising strategy for advancing CAR T-cell therapy in B-NHL (with 92% of study patients with LBCL). Prizlon-cel directly addresses antigen heterogeneity and loss, which are key drivers of resistance in single-antigen CAR T-cell therapies. Dual targeting of CD19 and

CD20 is a rational approach, as CD20 loss is relatively rare compared with CD19. Moreover, preclinical models have shown the bispecific design to be effective against both single-positive and double-positive tumor cells.

Dose-limiting toxicity was not observed, and the safety profile was manageable. Only 2.1% of infused patients developed grade 3 to 4 cytokine release syndrome, and none experienced grade 3 to 4 immune effector cell-associated neurotoxicity. The most common treatment-emergent adverse events were neutropenia (83.3%) and leukopenia (50.0%). With a median follow-up of 30 months, secondary primary malignancies were reported in 3 patients but were not considered related to prizlon-cel. These safety results compare favorably with those of currently approved anti-CD19 CAR T-cell products.

Although efficacy was not the primary end point of this phase 1 trial, the results were intriguing. The overall and complete response rates of 91.5% and 85.1%, respectively, surpass the outcomes reported in pivotal trials and real-world settings results for axi-cel, liso-cel, and tisa-cel in r/r LBCL. Notably, the durability of responses was particularly compelling: median progression-free survival (PFS) and overall survival (OS) were not reached, with 2-year PFS and OS rates of 62.6% and 76.5%, respectively. The study also provided insights into the pharmacokinetics of prizlon-cel. Robust expansion and long-term persistence of CAR T cells were observed, along with a significant correlation between higher peak CAR T-cell levels and improved clinical outcomes. However, manufacturing potency emerged as a critical factor, as diminished interferon-gamma release was associated with early progression in some patients. These findings underscore the importance of optimizing manufacturing processes to maximize therapeutic potential.

Although this trial provides strong preliminary evidence of prizlon-cel's efficacy and safety, several challenges remain. The study population predominantly consisted of patients without prior exposure to novel agents, such as bispecific antibodies or antibody-drug conjugates, which are increasingly used in r/r B-NHL. It remains unclear whether prizlon-cel can maintain its efficacy in heavily pretreated patients or those who have failed prior CAR T-cell therapies. Additionally, long-term safety data will require ongoing follow-up. Although secondary primary malignancies were rare and unrelated to prizlon-cel, the development of Epstein-Barr virus–positive cytotoxic T-cell lymphoma in 1 patient raises intriguing questions about the interplay between CAR T-cell therapy and preexisting clonal disorders.

With ongoing trials in both China and the United States, the global hematology community eagerly anticipates further validation of these findings. If prizlon-cel continues to demonstrate robust efficacy and safety in larger and more diverse patient populations, it could set a new benchmark for the durability and depth of response in CAR T-cell therapy for r/r B-NHL.

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**LYMPHOID NEOPLASIA**

*Comment on Gottschlich et al, page 1536*

# The immunotherapy real estate of Hodgkin lymphoma

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**In this issue of *Blood*, Gottschlich et al[1] present an in silico analysis of genomics data to highlight CD86 as a novel immunotherapeutic target in classic Hodgkin lymphoma (cHL). The authors explore the CD86-CTLA4 crosstalk axis between malignant Hodgkin Reed-Sternberg (HRS) cells and T cells in the tumor microenvironment (TME), and describe a CD86-28z chimeric antigen receptor (CAR) T-cell approach with promising preclinical in vivo efficacy.**