# CAR T-Cells for Cure in Pediatric B-ALL

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The first child to receive CD19 chimeric antigen receptor (CAR) T-cells has now been in a long-term remission—without interim therapy—for over a decade. This remission and early experience, followed by years of follow-up, served as a critical inflection point in pediatric B-cell acute lymphoblastic leukemia (B-ALL) therapy. Building on decades of collaborative efforts from pediatric oncologists worldwide, with iterative development of combinatorial chemotherapeutics, risk-stratification, incorporation of novel agents, and advances in supportive care, outcomes for childhood B-ALL are remarkably high. Nonetheless, given the prevalence of B-ALL, for those with relapsed/refractory disease, outcomes remained poor—making B-ALL among the leading causes of childhood cancer-related deaths.[1] Never before the advent of CAR T-cells could a single therapy in relapsed/refractory ALL both completely eradicate all evidence of disease *and* lead to long-term cure. Accordingly, the approval of tisagenlecleucel in 2017 was a tremendous advancement for children and young adults with relapsed/refractory B-ALL.

Now—a decade from the earliest experiences and 5 years from US Food and Drug Administration approval—we can reflect on lessons learned, evaluate longer-term outcomes, and identify current limitations and opportunities to overcome those. In the companions to this article, Laetsch et al[2] provided the 3-year update of the ELIANA registration study that led to approval for tisagenlecleucel while Wang et al[3] reported on the more contemporary strategy of coadministration of both CD19- and CD22-targeted CAR T-cells. The juxtaposition of these two manuscripts serve to firmly establish the critical and undeniable role of CAR T-cells in pediatric B-ALL while also illustrating current limitations, ongoing uncertainties, and the continued need to advance CAR T-cells in pediatric B-ALL.

In a highly anticipated follow-up from the phase II study of tisagenlecleucel in childhood B-ALL,[4] Laetsch et al[2] expanded on their original analysis to report on long-term outcomes. With a total of 79 patients infused and a median follow-up of 38.8 months, the overall remission rate was 82% (n = 65) at 3 months—which excluded four patients with initial response at day 28 but had either interval therapy (n = 1), relapse (n = 2), or experienced nonrelapse mortality (n = 1) before 3 months. The total and median event-free survival (EFS) for all patients was 44% (95% CI, 31 to 57) and 24 months and was not reached for those who achieved a complete remission (CR). The relapse-free survival with and without censoring for interim therapy (including hematopoietic stem-cell transplantation [HSCT]) was 52% (95% CI, 37 to 66) and 47.8% (95% CI, 34.4 to 60), respectively, at 36 months.

Although there were no major safety and toxicity concerns that emerged with this longitudinal follow-up, B-cell aplasia persisted in 71% and 59% of patients at 12 and 24 months, respectively, with a median time to B-cell recovery (in responders) of 35.3 months (95% CI, 22.9 to nonestimable). Importantly, they demonstrate a shorter duration of remission in those who lost B-cell aplasia in $< 6$ months postinfusion, emphasizing the critical role of CAR T-cell persistence in maintaining remission. As data from real-world utilization and longer follow-up are attained, these data will serve as critical benchmarks against which to compare contemporary results. While cementing the curative potential of CAR T-cells, the improvement in health-related quality-of-life over time (evaluated through quality-of-life studies in a subset of responders) also highlights the long-term tolerability of CAR T-cells, and incorporating such measures are exceedingly important given that these children may be long-term survivors.

Shifting gears to the role of combinatorial CAR T-cell strategies, Wang et al[3] explored the hypothesis that coinfusion of CD19- and CD22-targeted CAR T-cells would improve durable remission. Building on the fundamental principles and success of combination chemotherapy in pediatric B-ALL, efforts in dual antigen-targeting strategies are rapidly expanding. From the pioneering work with CD22 CAR T-cells[5] along with the pivotal CD19 CAR T-cell experience, combinatorial CD19 and CD22 CAR T-cell targeting is ready for prime time. Although a host of dual antigen-targeting strategies are being explored, coadministration, as presented in this study, offers the potential of using two constructs with established dual targeting functionality which may effectively synergize to eradicate populations with heterogeneous antigen expression to prevent antigen escape.

With an impressive accrual of 225 evaluable patients over a 2-year period (median age of 7.6 years), to our knowledge, this study represents the largest prospective CAR T-cell trial in children and young adults with B-ALL ever conducted. Among 194 patients with bone marrow involvement, 192 (99%) achieved a minimal residual disease–negative CR—with two patients dying from

ASSOCIATED CONTENT

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## THE TAKEAWAY

In the two articles that accompany this editorial,[2,3] we get both a longitudinal perspective on the use of CD19 chimeric antigen receptor (CAR) T-cells to achieve durable remissions in children and young adults with B-cell acute lymphoblastic leukemia along with insights for the role of combinatorial treatment approach with the infusion of two unique CAR T-cell products in optimizing remission rates. Collectively, these efforts strongly support the critically important role for CAR T-cells in children and young adults with B-cell acute lymphoblastic leukemia in achieving a cure—while laying a foundation for what future iterations of CAR T-cell–based approaches may look like to improve upon current outcomes.

CAR T-cell–associated toxicity. With 43 (22%) relapsing and a median follow-up of 11 months, the 12-month EFS was 73.5%. For 31 patients with isolated extramedullary relapse, all achieved a CR with a 12-month EFS of 68.6% (95% CI, 44.5 to 100). Although these results cannot be directly compared with ELIANA and single-agent tisagenlecleucel, the outcomes of coadministration of CD19 and CD22 CAR T-cells supports the potential of improved CR rates and durable remission—and longer follow-up is needed.

With the dual infusion, important insights are presented regarding in vivo engraftment, which occurred sequentially, first with CD19 CAR T-cells, then CD22 CAR T-cells, with earlier loss of the latter. With relapses skewing toward dual antigen positivity, given the median time to B-cell recovery of 74 days, this likely relates to overall shorter persistence—in contrast to the antigen-negative relapse predilection with the more persistent tisagenlecleucel in ELIANA.[4] In addition, the predilection of antigen-negative relapse to be predominantly $CD19^{negative}$ with retained CD22 expression suggests both that the kinetics and efficacy of the two various constructs differ and may vary on the basis of the antigen targeted.

The manufacturing for these dual products was centralized and generated from peripheral blood draws, rather than a leukapheresis, and manufactured over 7 days, with infusion of fresh product. The authors conclude that both the rapid vein-to-vein time and fresh infusion contributed to their remarkable results. In contrast to ELIANA, where 18.5% (18 of 97) of the enrolled patients dropped out before infusion,[4] only 2.6% (6 of 231) of eligible patients dropped out before dual CAR T-cell cell infusion. Although this is to be applauded, the feasibility of 1-week turnaround time and fresh infusions presents logistic challenges globally which may limit multicenter applicability using centralized manufacturing. Additionally, although coinfusion may be feasible, the financial burden of manufacturing two distinct products may be higher. With the remarkable ability to cure children, there remains a critical need for commitment to pediatric CAR T-cell development to optimize dual targeting CAR T-cell products and improve accessibility in a way that is both scalable and economical. Importantly, the majority of patients receiving dual CAR T-cell infusions were patients with first relapse, suggesting both the benefit of earlier use of CAR T-cells and highlighting a critical unmet need where further study is warranted, as first relapse is not an approved indication for tisagenlecleucel.

The role for consolidative HSCT after a CAR T-cell induced remission in children represents an area of ongoing debate,[6] particularly since the collective lack of random assignment to consolidative HSCT limits the interpretation of benefit seen with HSCT across CD19 CAR T-cell constructs.[7-9] With the desire to avoid short- and long-term toxicities associated with HSCT, avoiding HSCT is certainly understandable—but has to be balanced with risks of post-CAR T-cell relapse for which outcomes are poor.[10,11] Although there has been limited data on the role of consolidative HSCT after tisagenlecleucel, Laetsch et al[2] reported that data were available for eight of the 11 patients who underwent consolidative HSCT, all of whom remain in remission with a median of 18 months of follow-up. Wang et al[3] incorporated a planned consolidative HSCT for patients at risk for myeloid lineage switch (KMT2Ar/ZNF384r) (n = 24). However, along with performing HSCT in 54 additional patients because of parental preference, a total of 78 patients received consolidative hematopoietic cell transplantation. Ultimately those receiving HSCT had improved 12-month EFS compared with those not undergoing HSCT (85% *v* 69.2%), $P = .03$. Collectively, the emerging data suggests that consolidative HSCT will be needed in a proportion of patients to achieve cure, particularly in HSCT-naive patients and in those with short CAR T-cell persistence. Future efforts are needed to risk stratify and pre-emptively route high-risk patients to consolidative HSCT for relapse prevention. Preinfusion disease burden, in particular, warrants close study given its impact on EFS.[12,13]

In conclusion, spanning the era from 2015 to 2021, these two manuscripts showcase the current state of art in CAR T-cells for pediatric B-ALL. Cure, particularly for those in whom it was deemed impossible, is within reach. Contrasting to contemporary outcomes in less heavily pretreated patients with first relapse, where the 2-year disease-free survival was 54.4% using an intensive chemotherapy backbone with blinatumomab and an intention of consolidative HSCT,[14] the comparable outcomes of CAR T-cells with substantially lower

toxicity in a more heavily treated population serves to further emphasize the incredible role of CAR T-cell therapy. Nonetheless, the 3-year EFS of 44% after tisagenlecleucel serves as a reminder that there remains opportunity for improvement. There is reason for optimism that iterative improvements with CAR T-cell strategies will enable even higher rates of durable remission. And until we cure 100% of children with B-ALL, our work will not be done.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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