Chimeric Antigen Receptor T-Cell Therapy Clinical Results in Pediatric and Young Adult B-ALL

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Abstract
Chimeric antigen receptor (CAR)-modified T-cell therapy has revolutionized the care of patients with relapsed and refractory B-cell acute lymphoblastic leukemia (B-ALL). Results from clinical trials across multiple institutions report remarkable remission rates with CD19-directed CAR-modified T-cell therapy. These remissions are also proving to be durable in many patients with a relapse-free survival (RFS) of approximately 50% to 60% at 1 year across several trials and institutions in this population that has been historically very difficult to treat. In addition, new products are being developed to enhance upon the original CART-cell products, which include a humanized CAR, allogeneic CARs, and both CD22 and biallelic CD19 and CD22 constructs. Toxicity after CAR-modified T-cell therapy is characterized by cytokine release syndrome (CRS) and neurotoxicity in the acute post-infusion period and B-cell aplasia as a long-term consequence of treatment. This review will summarize the published data thus far on the use of CAR-modified T-cell therapy in pediatric B-ALL and outline the various CAR products now being developed for this population. Delivery of this therapy and the decision to pursue hematopoietic stem cell transplant (HSCT) after treatment will be discussed.

Introduction
Acute leukemia is the most common malignancy in pediatrics, comprising approximately 30% of all cancer in this population.1 B-cell acute lymphoblastic leukemia (B-ALL) is the most common acute leukemia in childhood. The overall survival (OS) for children diagnosed with B-ALL has increased dramatically in the last few decades and now approaches 90%.2-5 However, this success is not shared with patients who suffer from relapsed disease. Outcomes vary based on timing from initial diagnosis to relapse, site of relapse, leukemia immunophenotype, and response to re-induction therapy. For patients across these spectrums, the overall survival is 35% to 40% after treatment with traditional cytotoxic chemotherapy, which is significantly lower for patients who relapse after hematopoietic stem cell transplant (HSCT) or who require more than one salvage attempt.6,7 Despite numerous relapse treatment regimens implemented over time, these outcomes have largely not changed.

Relapsed leukemia therapy also is accompanied by significant toxicity. Re-induction treatment courses are both immunosuppressive and myelosuppressive. With deaths attributed to toxicity reported at 4% to 5%, the current regimens cannot be safely intensified.8 HSCT is a component of relapsed therapy for patients with early medullary relapse and those patients with second or greater relapse in a deep remission.8 HSCT is associated with significant morbidity and mortality. The poor potential for salvage and the real risk of toxicity with cytotoxic therapy in patients with relapsed leukemia indicates that novel agents are needed to achieve better outcomes for this population.

Immunotherapy has shown great promise in B-ALL as an alternative approach to cytotoxic chemotherapy in patients with relapsed and refractory disease. In particular, chimeric antigen receptor (CAR)-modified T-cells that target CD19 have demonstrated remarkable remission rates. Short-term toxicity is serious but recoverable. Hypogammaglobulinemia as a result of B-cell aplasia is the primary long-term side effect reported and is well-managed with regular immunoglobulin replacement. This review will summarize the data thus far for CD19-directed CAR-modified T-cell therapies in children and young adults, discuss the additional CAR products available in B-ALL, outline the logistics around delivery of CAR-modified T-cells, and review the toxicity associated with treatment with these agents.

CAR construct
CARs connect an intracellular signaling domain, the CD3ζ domain of the T-cell receptor (TCR) complex, to an extracellular domain that serves to recognize antigen. This extracellular component originates from a monoclonal antibody single chain variable fragment (scFv).9,10 The first CARs developed included only a single signaling domain. These, later named, “first generation” CARs performed poorly in clinical trials with little...
efficacy, as they demonstrated weak proliferation and persistence in the circulation after infusion.11 “Second generation” CAR constructs, including an additional costimulatory domain, typically CD28 or 4-1BB, were the first to achieve significant expansion, resulting in notable clinical activity. “Third generation” CARs incorporating 2 costimulatory domains are being developed and studied but have yet to demonstrate improved activity.9,12 The addition of the costimulatory domains to the intracellular signaling structure is responsible for the proliferation and persistence of the CAR-modified T-cells, both of which are necessary to induce a clinical response.9,12

### CD19-directed CAR T-cells

The University of Pennsylvania (Penn) was the first to report successful use of CD19-targeted CAR-modified T-cell therapy in an adult patient with refractory chronic lymphocytic leukemia (CLL).13 With a second generation CAR using the 4-1BB costimulatory domain (CTL019, now known as tisagenlecleucel or KymriahTM), this patient achieved remission and B-cell aplasia, which was sustained at 10 months at the time of publication. The first use of CAR-modified T-cell therapy in pediatrics was reported by Penn and the Children’s Hospital of Philadelphia (CHOP) in 2 children with relapsed and refractory B-ALL using the same CAR construct as the first adult patient treated with CLL. Both pediatric patients achieved a minimal residual disease (MRD) negative (<0.01%) remission one month after the infusion.14 This early success was replicated in several single-institution phase one clinical trials in both children and adults and in both B-ALL and non-Hodgkin lymphoma (NHL). This review will focus on data from trials conducted at pediatric institutions treating children and young adults with B-ALL (Table 1).

In 2014, Penn and CHOP reported early data on the first 30 pediatric and adult patients with ALL treated with CTL019. Ninety percent of patients achieved a complete remission (CR) one month post-infusion. Six months after infusion, the event-free survival (EFS) was 67% (95% confidence interval (CI) 51 to 88%), and the overall survival (OS) was 78% (95% CI 65 to 95%).15 The National Cancer Institute (NCI) reported on 20 pediatric and young adult patients with B-ALL infused with CD19-CAR T-cells containing a CD28 costimulatory domain with an intention-to-treat analysis. CR rate at 1 month was 70% (95% CI 45.7 to 88.1%), and OS, with a median of 10 months of follow up, was 51.6%.16 Gardner et al described the experience at Seattle Children’s treating 43 pediatric and young adult patients with CD19-directed CAR T-cells containing a 4-1BB costimulatory domain. Ninety-three percent of infused patients achieved MRD negative CR by 21 days after infusion. They estimated a 12-month EFS of 50.8% (95% CI 36.9 to 69.9%) and OS of 69.5% (95% CI 55.8 to 86.5%) with a median follow-up of 9.6 months.17 CAR-modified T-cells were detected in the cerebrospinal fluid (CSF), and patients with documented leukemia in their CSF who had a bone marrow response to CD19 CAR T-cells also had clearance of disease in their CSF across these trials.14–17 The outcomes of these clinical trials at three different institutions with distinct CAR-modified T-cell products produced in 3 separate laboratories are notably all very similar.

Updated data with longer follow-up was presented at the American Society of Hematology and the American Society of Clinical Oncology annual meetings. Penn/CHOP reported a CR rate of 93% in 60 children and young adults treated with CTL019. Relapse-free survival (RFS) was 60% (95% CI 48 to 75%) and OS 79% (95% CI 67 to 88%) at 12 months with a median follow up of 15 months. Continued B-cell aplasia was observed in 24 out of 34 patients in ongoing CR with the longest follow up being 48 months post-infusion.18,19 The NCI reported a CR rate of 60.8% in 51 patients treated with CD19-CAR T-cells, with a median leukemia-free survival of 18 months.20

CTL019 received Breakthrough Therapy designation by the Food and Drug Administration (FDA) in 2014. A phase 2 multicenter, global registration trial (ELIANA) was conducted to assess feasibility, safety, and efficacy. Patients were enrolled across 25 centers in the United States, Europe, Canada, Australia, and Japan. It was the first CAR trial that dispensed industry-manufactured cells across a global supply chain.19,21 Seventy-five patients were infused with CTL019, and 81% of patients were in MRD-negative remission by 3 months. At 6 months, the EFS was 73% (95% CI 60 to 82%), and the OS was 90% (95% CI 81 to 95%). At 12 months, the EFS and OS were 50% (95% CI 35 to 64%) and 76% (95% CI 63 to 86%), respectively. CAR-modified T-cells persisted in the circulation up to 20 months with a median of 168 days at data cutoff.22 Based on data from the ELIANA trial, with supporting data from the Penn/CHOP phase 1/2a trial and a US multicenter phase 2 trial, CTL019 was granted FDA approval as tisagenlecleucel (KymriahTM) on August 30, 2017.

### Alternative CAR-modified T-cell products for B-ALL

Most scFv domains incorporated into existing CAR T-cell products are of murine derivation. It is hypothesized that anti-mouse immune rejection can contribute to poor CAR T-cell persistence in some patients, and cases of cellular immunogenicity to the CAR have been reported.23 To avoid that immunemediated response, a humanized anti-CD19 scFv was developed by the Penn/CHOP group in collaboration with Novartis, and the

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**Table 1**

| Outcomes for Children and Young Adults Across CD19-directed CAR-modified T-cell Clinical Trials. |
|----------------------------------------|
| **Penn/CHOP Phase 1/2a**15,19 | **NCI Phase 1**19,26 | **Seattle Phase 1/2**17 | **Global Phase 2 of CTL019**22 |
| **Number of patients treated** | 6019 | 5120 | 43 | 75 |
| **CR rate** | 93%19 | 60.8%20 | 93% | 81% |
| **EFS/RFS/LFS** | 60% RFS at 12 mo (95% CI 48–75)%19 | 49.5% LFS at 18 mo20 | 50.8% at 12 mo (95% CI 36.9–69.9) | 73% at 6 mo |
| **CAR T-cell persistence** | 68% at 6 mo*(95% CI 50–92)%15 | 68 days**16 | Median 3 mos*** | Median 168 days (range 20–617) |

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*CR = complete remission, EFS = event-free survival, LFS = leukemia-free survival, mo = months, RFS = relapse-free survival.
**Probability of persistence.
***Longest duration in any patient.

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the activator-like effector nuclease (TALEN) technology to remove an allogeneic CD19 CAR T-cell product that uses transcription CD22 site density was associated with 7/8 relapses.30 In initial remission duration of 6 months. These responders included 5 out of 13 patients achieved remission and no graft-versus-host disease (GVHD) was observed.26 While this approach addresses the problem of lymphopenia, it nonetheless requires an individualized manufacturing. To overcome this obstacle and increase accessibility, a completely engineered product that does not require an individual patient, which translates to an expected waiting period prior to treatment as the product is being manufactured. Finally, collected T-cells must be robust to undergo the manufacturing process and have the potential to replicate once reinfused into the patient. Every patient is not able to produce these healthy T-cells, most often due to lymphopenia secondary to pre-treatment with chemotherapy and/or HSCT. For all of these reasons, a CAR T-cell product from an allogeneic donor is an attractive alternative. These products have been studied in adult patients who relapsed after HSCT using T-cells from these patients’ stem cell donors. Eight out of 20 patients achieved remission, and no graft-versus-host disease (GVHD) was observed.26 While this approach addresses the problem of lymphopenia, it nonetheless requires an individualized manufacturing. To overcome this obstacle and increase accessibility, a completely “off-the-shelf” product that does not require HLA matching and can be mass-produced for multiple patients is an attractive alternative under study. GVHD is a major concern with using an “off-the-shelf” product, and these worries were confirmed in preclinical models.27 Cellectis has developed an allogeneic CD19 CAR T-cell product that uses transcription activator-like effector nuclease (TALEN) technology to remove the αβ T-cell receptor to mitigate the risk of GVHD.28 The first use of this product was reported in 2 infants with relapsed B-ALL.29 While activity is encouraging, limitations remain, including the potential for GVHD with incomplete ablation of the TCR and rejection due to HLA mismatch limiting persistence. Clinical trials with this product are ongoing.

In addition to CAR-modified T-cell products that target CD19, CARs directed against CD22 have also been developed and are under study in pediatrics. The NCI reported their results from a phase one dose escalation trial using CD22 CAR modified T-cell therapy in 21 children and adults.30 Complete remissions were observed in 73% of patients (11 out of 15) treated with a dose ≥ 1 × 10^6 which is the same active dose of CD19 CARs, with a median remission duration of 6 months. These responders included 5 out of 5 patients with CD19 dim to negative leukemia. Diminished CD22 site density was associated with 7/8 relapses.30 In initial trials, CD22 CAR-modified T-cells primarily have followed CD19 CAR T-cells in those patients with CD19-positive or CD19-negative relapse. To obviate antigen escape that is now well characterized in both CD19 and CD22 directed CAR products, development of products that target both CD19 and CD22 are ongoing.31

Delivery of CAR-modified T-cell therapy

Lymphodepleting chemotherapy

Most institutions administer CAR-modified T-cell therapy following a course of lymphodepleting (LD) chemotherapy that most commonly consists of fludarabine and cyclophosphamide.15-17,20 Lymphodepletion serves to provide both leukemia control and immunosuppression, which facilitates the homeostatic expansion of CAR T-cells. The NCI compared multiple LD chemotherapy regimens: low dose fludarabine (2.5 mg/m²/day for 3 days) and cyclophosphamide (900 mg/m² once) for patients with a low B-ALL disease burden vs fludarabine, cytarabine, and GCSF, ifosfamide and etoposide, or higher dose fludarabine (30 mg/m²/day for 4 days) and cyclophosphamide (1200 mg/m²/day for 2 days) for patients with a higher B-ALL disease burden. They found that use of fludarabine and cyclophosphamide as the LD chemotherapy regimen at both dose levels correlated with higher OS (13.3 months with a 34.7% probability of survival starting at 38 months vs 5.5 months without any survivors past 11 months).20 Gardner et al similarly found that fludarabine and cyclophosphamide was superior to other regimens. In their Seattle cohort, they found that the duration of B-cell aplasia was longer at 6.4 months (95% CI lower bound 2.5 months) for the 14 patients who received fludarabine and cyclophosphamide as LD chemotherapy when compared to 2.1 months (95% CI 1.4 to 6.4 months) in the 29 patients who did not receive that regimen.17

Augmenting response with reinfusion and pembrolizumab

The minimal duration of CAR T-cell persistence necessary to result in durable remission is unknown and may vary among CAR constructs and individual patients. However, B-cell recovery has been associated with a higher risk of CD19+ relapse.17 Reinfusions have been performed for early B-cell recovery and CD19+ MRD with mixed responses. The Seattle and NCI groups have shown limited effect with reinfusion, while we have demonstrated prolonged persistence and remission re-induction with reinfusion of CTL019 or CTL119.16,17,32 Pembrolizumab (PEM), a PD-1 checkpoint pathway inhibitor, has also been used with reinfusion to improve CAR T-cell expansion and persistence. Early data of use of reinfusions with PEM in 6 pediatric patients was reported at the American Society of Clinical Oncology annual meeting in 2017. PEM was administered 14 days to 2 months after CAR T-cell infusion with increased and/or prolonged CAR T-cell presence in the circulation in 5/6 with objective responses in 3/6 children. Importantly, PEM was well tolerated with no serious adverse events reported.33

To transplant or not to transplant?

A consensus on the necessity of HSCT after treatment with CAR-modified T-cell therapy does not exist. Practices vary across institutions, the CAR construct used and expectation of
Cytokine release syndrome

The intense immune activation stimulated by exponential CAR T-cell proliferation produces a constellation of symptoms called cytokine release syndrome (CRS). It has been described after treatment with monoclonal antibodies, such as rituximab (anti-CD20) and alemtuzumab (anti-CD52), and bi-specific T-cell-engaging antibodies, such as blinatumomab and, most recently, with CAR T-cell therapy. The symptoms appear at various timelines specific to the inciting immunotherapy. CRS associated with CAR T-cell therapy is secondary to T-cell proliferation; therefore, the timecourse parallels that of maximal T-cell expansion, which can vary from a few days to 2 weeks after infusion. 

Clinical symptoms reflect systemic inflammation and span a spectrum from fever, headache, and myalgias to unstable hypotension and multisystem organ failure, including respiratory failure, cardiac dysfunction, hepatic toxicity and coagulopathy. While the severity of illness can be significant and life-threatening in approximately 25% of patients, almost all patients recover without lasting sequela. Effort has been made to predict which patients will experience severe CRS. High disease burden prior to infusion of CAR-modified T-cells was consistently associated with severe CRS across studies. 

Comparing incidence of CRS across CAR T-cell constructs and institutions is limited by the use of different CRS grading systems. The Common Terminology Criteria for Adverse Events (CTCAE) CRS grading was most applicable to infusional reactions and proved inapt for CRS associated with CAR T-cell therapies. CTCAE version 5 CRS grading is updated to broaden the applicability. However, to more accurately report CRS, several groups developed CRS grading scales for clinical trials of their CAR T-cell products (Table 2). In the NCI CRS grading system, Grade 2 CRS includes oxygen supplementation <40% or hypotension responsive to fluids or low-dose vasopressors.

### Table 2

| Cytokine Release Syndrome Grading Systems. | NCI34 | Penn/CHOP45 | CTCAE, v539 |
|------------------------------------------|-------|-------------|-------------|
| Grade 1 Symptoms are not life-threatening and require symptomatic treatment only | | | |
| Grade 2 Symptoms require and respond to moderate intervention: oxygen requirement <40% or hypotension responsive to fluids or low-dose vasopressor or grade 2 organ toxicity | Mild reaction: treated with supportive care | Moderate reaction: some signs of organ dysfunction related to CRS and not attributable to other conditions. Hospitalization for management of CRS-related symptoms, including fevers with associated neutropenia, need for IV therapies | Fever with or without constitutional symptoms |
| Grade 3 Symptoms require and respond to aggressive intervention: oxygen requirement ≥40% or hypotension requiring high dose or multiple vasopressors or grade 5 organ toxicity or grade 4 transaminites | More severe reaction: hospitalization required for management of symptoms related to organ dysfunction related to CRS and not attributable to other conditions, includes hypotension treated with intravenous fluids or low-dose vasopressors, coagulopathy requiring fresh frozen plasma or cryoprecipitate or fibrinogen concentrate, and hypoxia requiring supplemental oxygen | Hypotension managed with one vasopressor; hypoxia requiring ≥40% oxygen |
| Grade 4 Life threatening symptoms: requirement for ventilator support or grade 4 organ toxicity (excluding transaminites) | Life-threatening complications such as hypotension requiring high-dose vasopressors, hypoxia requiring mechanical ventilation | Life-threatening consequences; urgent intervention indicated |

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Grade 3 CRS consists of oxygen requirement ≥40% or hypotension requiring high-dose or multiple vasopressors, and grade 4 CRS consists of the requirement of ventilatory support or grade 4 organ toxicity (excluding transaminitis). The NCI reported 14% (3/21) grade 3 CRS and 14% (3/21) grade 4 CRS in their published CD19 CAR-modified T-cell treated cohort. The Penn/CHOP CRS grading scale defines hypotension requiring IV fluid boluses or low dose vasopressors as grade 3. Grade 3 CRS also includes coagulopathy requiring transfusions or hypoxemia requiring high-flow oxygen or noninvasive mechanical ventilation. Grade 4 is defined as life threatening and includes hypotension requiring high dose vasopressors or hypoxemia requiring invasive mechanical ventilation. Out of 39 patients treated with CTL019 on the CHOP/Penn phase 1/2a trial and evaluated by Fitzgerald et al, 7 (18%) developed grade 3 CRS and 11 (28%) grade 4. On the ELIANA phase 2 global registration trial of CTL019, 21% (16/75) developed grade 3 CRS and 25% (19/75) grade 4 CRS. The Seattle group defined severe CRS as requiring vasopressors or inotropes or developing respiratory failure. Ten of their 43 treated patients (23%) developed severe CRS. Notably, no patient in their cohort required intubation for respiratory failure or multiple or high-dose pressors.

These symptomatology and laboratory findings mirror those found in the disease spectrum of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH). Consequently, early decisions in management of CRS were modeled after what is known about cytokine drivers of MAS/HLH. Care needs to be taken to rescue patients from organ failure or multiple or high-dose pressors.8 Potentially lethal events are histologically similar to severe CRS and are often termed as life threatening and includes neurotoxicity development. Fatal cerebral edema, which has been observed in adults treated with the 19–28z CAR, is thought to be a distinct process and has not been reported in pediatric trials.

### B-cell aplasia

CD19 is a ubiquitous B-cell marker, present on the surface of B-cells throughout maturation; therefore, it is an excellent target for B-cell malignancies. The current CAR T-cell products available cannot distinguish between malignant and normal B-cells; therefore, all B-cells are targeted and removed by these therapies. B-cell aplasia is a long-term toxicity that results in agammaglobulinemia and persists as long as CD19 CAR T-cells are present and functional in the patient. This expected toxicity can serve as a proxy for CD19 CAR T-cell functional persistence after treatment.

### Antigen escape

While the outcomes have been encouraging for so many patients with CD19-directed CAR-modified T-cell therapy, a subset of patients will go on to relapse after this treatment. Lack of persistence of CAR T-cells, which leaves the circulation without leukemia surveillance, is one mechanism of relapse. The other way the leukemia can return is through a CD19-negative relapse.46 In those cases, CAR-modified T-cell persistence and B-cell aplasia can be ongoing, but leukemic blasts with lost CD19 epitope escape the targeted therapy. Every trial that has studied this therapy has reported this outcome in a subset of patients. Another evasion technique that has been described in the literature is a leukemic lineage switch from lymphoid to myeloid with, again, loss of the CD19 epitope. This phenomenon is associated with leukemia characterized by the KMT2A gene rearrangement.

### Conclusions

CD19-directed CAR-modified T-cell products have been transformational in pediatric B-ALL, resulting in long-term remissions for many refractory and relapsed patients that historically had no available alternative treatments with curative intent. The FDA and EMA approvals of tisagenlecleucel will improve access to this therapy, but continued work needs to be done. The variations in persistence of CAR-modified T-cells across CAR constructs and
individual patients needs to be better understood and addressed. Methods to overcome and prevent antigen escape need to be developed. More data on the humanized constructs and CARs directed against CD22 and bispecific CARs should be forthcoming. The CAR landscape is quickly growing and evolving, and optimism continues for those developments ahead.

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