The Future of Cellular Immunotherapy for Childhood Leukemia

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Abstract

Purpose of review: Exciting translational discoveries in recent years have brought realized promise of immunotherapy for children with high-risk leukemias. This review summarizes the current immunotherapeutic landscape with a focus on key clinical trials for patients with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML).

Recent findings: Chemotherapy resistance remains a major barrier to cure in children with high-risk leukemias. Immunotherapy approaches have potential to overcome this resistance given alternative mechanisms of action. Based upon preclinical activity and/or success in adult patients, recent clinical trials have demonstrated safety and efficacy of various monoclonal antibody, antibody-drug conjugate, bispecific T cell-engaging antibody, natural killer cell, and chimeric antigen receptor-redirected T cell immunotherapies for children with ALL or AML. Food and Drug Administration approval of several of these immunotherapies has increased the pediatric leukemia therapeutic portfolio and improved clinical outcomes for previously-incurable patients.

Summary: Several antibody-based or cellular immunotherapy modalities have demonstrated appreciable efficacy in children with relapsed or chemotherapy-refractory leukemia via early-phase clinical trials. Some studies have also identified critical biomarkers of treatment response and resistance that merit further investigation. Continued preclinical and clinical evaluation of novel immunotherapies is imperative to improve cure rates for children with high-risk leukemias.

Keywords

antibody; cellular therapy; childhood leukemia; immunotherapy

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INTRODUCTION

Though improved therapeutic regimens and supportive care for children and adolescents with B-cell acute lymphoblastic leukemia (B-ALL) now achieve relapse-free survival (RFS) of >90%, those with relapsed or chemotherapy-refractory disease remain difficult to cure. Pediatric patients with acute myeloid leukemia (AML) continue to have unacceptably lower cure rates of approximately 60% despite maximally-intensive chemotherapy and often subsequent myeloablative hematopoietic stem cell transplantation (HSCT). The advent of effective immunotherapy is now changing therapeutic paradigms, providing options for patients in whom cytotoxic chemotherapy has proven ineffective or intolerable. Immunotherapies can be exquisitely target-specific, conferring more limited toxicity to normal tissues than traditional chemotherapy drugs. Given their alternative mechanisms of action, immunotherapy agents can often be combined with chemotherapy to increase curative potential. In this review, we concisely describe major immunotherapy modalities under preclinical or current clinical study for children and adolescents/young adults (AYAs) with relapsed/refractory ALL and AML (Figure 1) and highlight the potential of these new approaches to improve outcomes.

ANTIBODY-BASED IMMUNOTHERAPY

Monoclonal Antibodies

The exquisite specificity of monoclonal antibodies (moAbs) binding to target antigens can result in effective depletion of antigen-expressing malignant blasts ('on-target/on-tumor' effects), although depletion of antigen-expressing normal cells ('on-target/off-tumor' effects) can also occur. While moAb therapies are rarely used in current treatment of children with ALL and AML, they have provided an important biologic foundation for 'next generation' antibody-based immunotherapies described below. A current phase 1/2 clinical trial is assessing the safety and potential efficacy of the anti-CD38 moAb daratumumab with chemotherapy in pediatric patients with relapsed B-ALL or T-ALL (NCT03384654) based upon activity in preclinical models (1).

Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) are comprised of moAbs linked to cytotoxic drug 'payloads' and have been used in treatment of children with AML and B-ALL. The ADC gemtuzumab ozogamicin (GO) connects a CD33 moAb to the toxic antibiotic calicheamicin via an acid-labile linker, which facilitates its release upon GO internalization into CD33+ cell lysosomes (2). GO has been extensively studied in patients with AML (3–17) and is now Food and Drug Administration- (FDA) and European Medicines Agency (EMA)-approved for adults with relapsed or *de novo* disease and for children with relapsed/refractory disease. GO was initially studied in children with AML as monotherapy and then in combination with chemotherapy via several Children's Oncology Group (COG) and European consortia trials (4, 5, 7–10, 14, 17, 18). Superior RFS with GO addition to chemotherapy was observed in some children with *de novo* AML treated on the COG phase 3 AAML0531 study (19). Based on these and other data, GO will be incorporated into frontline therapy for children and AYAs with CD33+ AML on the successor phase 3 AAML1831 trial. Other

myeloid antigen-targeting ADCs (*e.g.,* IMGN-632 targeting CD123, anetumab ravtansine targeting mesothelin) are under clinical evaluation in adults with AML (NCT03386513) and with pediatric phase 1 trials planned.

Inotuzumab ozogamicin (InO) is a similar ADC that links a CD22 moAb to calicheamicin and is now FDA- and EMA-approved for adults and children with relapsed/refractory B-ALL after demonstration of safety and efficacy (20–25). In the pediatric realm, InO was initially trialed in five children with multiply-relapsed B-ALL with responses reported in three patients (22). These encouraging results were followed by extended pediatric access to InO. A retrospective analysis of 51 children with relapsed/refractory B-ALL treated with InO reported complete morphologic responses (CR) in 67% of patients, 71% of whom achieved minimal residual disease (MRD)-negative remission (24). In this study, CD22 downregulation on leukemia cells was suggested as a mechanism of therapeutic evasion, although antigen expression levels were not systematically quantified (24). The potential safety and efficacy of InO treatment of children and AYAs with relapsed/refractory B-ALL is under current evaluation in the COG phase 2 AALL11621 trial (NCT02981628).

Due to their calicheamicin payloads, GO and InO have potential for hepatic toxicity with sinusoidal obstructive syndrome (SOS), particularly when administered in close proximity to HSCT. Although high rates of SOS were initially reported in adult patients with AML treated with GO (26), multiple pediatric clinical trials have not demonstrated increased SOS incidence in GO-treated children with relapsed or *de novo* AML (9, 10, 12, 14, 16, 18). The AALL1621 study is carefully monitoring rates and severity of SOS in children with relapsed/refractory B-ALL treated with InO.

Bispecific T cell-engager molecules

Technological advances in protein engineering have led to development of immunotherapeutic agents capable of binding tumor-specific targets while simultaneously activating endogenous immune effector T cells. Bispecific T-cell engager (BiTE) molecules consist of single-chain variable fragments (scFvs) derived from linked heavy and light chains of moAbs specific for tumor-associated antigens that are fused to a second scFv specific for the T-cell receptor (TCR) CD3ε component and promote formation of an effective immunological synapse (27). Given their extremely short half-lives (28), blinatumomab and other BiTEs require administration via continuous intravenous infusion, which may pose quality-of-life issues for some patients. The safety and activity of the CD19xCD3 BiTE blinatumomab has been demonstrated in adults and children with relapsed/refractory B-ALL in several studies (29–33), which led to FDA and EMA approval in 2018. An international phase 1/2 trial of blinatumomab in children with relapsed/refractory B-ALL determined recommended pediatric dosing of blinatumomab and reported a CR rate of 37% after up to two cycles (33). Ongoing studies are assessing potential biomarkers of treatment response and failure (34). Blinatumomab is under additional pediatric evaluation in the relapsed and newly-diagnosed settings in the COG AALL1331 (NCT02101853) and AALL1731 (NCT03914625) trials, respectively.

BiTEs targeting myeloid antigens (*e.g.*, CD33, CD123, FLT3R [CD135]) are also under early-phase clinical evaluation for adults with AML (NCT02520427, NCT03224819,

NCT03541369, NCT03739606, NCT02152956). The PEPN1812 phase 1 trial of the CD123xCD3 dual affinity-retargeting antibody flotetuzumab for children and AYAs with relapsed/refractory AML will open soon via the Pediatric Early Phase Clinical Trials Network.

NON-ENGINEERED CELLULAR THERAPIES

T cell therapies

Pioneering studies reported that T cells with specific activity against cells infected with virus (viral-specific T cells [VSTs]) can be identified in peripheral blood and used to treat infection and virus-associated malignancy even when host immunity is ineffective (35–38). Similar to VSTs, circulating leukemia-specific T cells have been identified, can be isolated *ex vivo*, and have shown activity against ALL (39). Several groups have now proven safety and feasibility of this approach with single and multiple-antigen specific cells generated and infused into patients for treatment or prevention of leukemia relapse (40–42), although responses against high-burden disease have not been observed. Combinatorial therapy with leukemia-specific cells and immunosuppressive checkpoint inhibitors may ultimately be most effective, and such strategies are being actively explored.

NK cell therapies

Patients with leukemia have known deficiencies in NK functionality, which include lack or downregulation of NK cytotoxicity receptors (43–45), diminished killing capacity (46, 47), and altered microRNA expression (48, 49). Complete replacement of the dysfunctional NK lineage is possible with HSCT, which confers significant toxicity risk. Alternatively, *ex vivo* activation, expansion, and infusion of patient-derived NK cells (50) has proven safe, albeit with limited anti-tumor efficacy to date (51–59). Achieving effective *in vivo* NK cell doses remains a challenge in delivering NK cell therapy to patients with acute leukemias, and improved expansion and proliferation techniques are needed.

ENGINEERED CELLULAR THERAPIES

Chimeric antigen receptor (CAR) T cell therapies

CD19 and CD22 CAR T cells for B-ALL—Technological advances in cellular engineering and improved biologic understanding (60) have contributed to the rapid development and clinical success of autologous CD19-redirected chimeric antigen receptor (CAR) T cell for patients with multiply-relapsed/chemorefractory B-ALL (61–65). CARs are synthetic receptors comprised of an extracellular scFv-based domain that binds a tumor-specific surface antigen, a hinge, a transmembrane domain, and one or more intracellular signaling domains that confer activation, proliferation, and/or survival signals to (usually virally-transduced) T cells. Though first developed as a tool to divorce HLA restriction from inherent T-cell biology (66), autologous CAR T cells have quickly demonstrated potent and paradigm-changing therapeutic efficacy, as reflected by accelerated clinical development and FDA and EMA approval of some products (67). The first CAR T cells were designed against solid tumors and contained a single T-cell activation domain (CD3ζ) (68). It was subsequently realized that incorporation of a second intracellular T cell signaling domain

(*e.g.*, CD28, CD137) to provide co-stimulation resulted in greater proliferative capacity, anti-tumor efficacy, and *in vivo* persistence (69–71). These 'second-generation' CAR T cells targeting CD19 and/or CD22 have now shown robust efficacy in children with relapsed/ refractory B-ALL (61–64, 72, 73).

Clinical experience and challenges with CD19 CAR T cell (CD19CART) testing in children with B-ALL have been comprehensively reviewed elsewhere (74, 75). Recently, CD22CART approaches have been developed to overcome CD19-negative leukemia relapses now known to occur at high frequency after CD19CART or blinatumomab therapy (described in detail below) (75–79). Initial data from an ongoing pediatric phase 1 study (NCT02315612) reported a 73% CR rate at 28 days post-CD22CART, although 14 of 17 patients subsequently relapsed (73). Allogeneic 'off-the-shelf' CD19CART approaches (80) are also under early-phase evaluation in adults and children to circumvent issues of suboptimal autologous T cell pheresis in heavily chemotherapy-myelosuppressed patients and to decrease timing to infusion (NCT03190278). Because of the clinical efficacy of CD19CART cells, rapid US and international development has occurred. This widespread interest is evident in the extensive number and location of active clinical trials (Table 1, Figure 2).

CAR T cells for AML—Successful CAR T cell development for children and AYAs with myeloid leukemias has proven challenging given lack of identified 'universal' AML antigens and appreciable risk of both hematologic and non-hematologic on-target/off-tumor toxicity (81, 82). Several phase 1 clinical trials of CD33CART or CD123CART are underway in adults with AML after promising preclinical data (83–98) (NCT03126864, NCT03904069, NCT02159495, NCT03766126); some of these trials now allow older pediatric patient participation (Table 2). Additional pediatric-specific institutional phase 1 trials of CAR T cells targeting CD33 (NCT03971799), CD123, CD135 (FLT3R), and CD371 (CLEC12A) are in development with other preclinical studies ongoing.

CAR T cell resistance: antigenic modulation—Data from pediatric and adult phase 1 trials have now highlighted major potential mechanisms of immunotherapeutic resistance in children with B-ALL (99). One study reported B-ALL cell CD19 splice variants (either *de novo* or after CD19CART therapeutic pressure) that result in loss of the CAR binding epitope and surface antigen expression (76, 100). Loss of CD81, a CD19 chaperone, also results in cytoplasmic retention of CD19 that prevents CD19-targeted immunotherapy activity (101, 102). Immune escape via CD22 surface protein downregulation after CD22CART can also occur (73). Finally, lymphoid-to-myeloid lineage switch after CAR T cell or BiTE immunotherapy has been reported (78, 79).

Dual antigen-targeting CAR T cells developed to combat immunotherapeutic resistance are under active exploration; studies of CD19xCD20CART or CD19xCD22CART have shown preliminary safety and efficacy in a small number of patients with relapsed/refractory B-cell malignancies (NCT03241940, NCT03330691) (72). Alternative 'syn-notch' approaches coupling target recognition by a constitutively expressed CAR to transcriptional expression of a second chimeric receptor require surface expression of both antigens for effective T-cell mediated cytotoxicity (103). In this system, initial target recognition induces cleavage of a

transcription factor, which then drives expression of another CAR that binds a distinct tumor-associated target. Such strategies remain under preclinical evaluation and have not yet been tested in patients.

CAR-NK cell therapies

While CAR-T cell production from patient- and donor-derived peripheral blood mononuclear cells is becoming more accessible, engineering of other immune effector cell types is also evolving. The use of artificial antigen- and cytokine-presenting cells (104, 105) to stimulate NK cell activation and expansion has allowed for *ex vivo* culture and genetic modification of innate effector cells. In contrast to adoptively-transferred CAR T cells that can persist for years in patients (106), NK cells with their shorter *in vivo* persistence induce far more limited on-target/off-tumor toxicity, which may allow targeting of a greater number of potential tumor antigens. Another benefit of NK cell-based therapies is their inability to cause graft-versus-host disease given lack of cell surface TCRs (107). As such, the therapeutic potential of CAR-NK cells could be far greater than autologous CAR T cell approaches (97, 108–111), as multiple cell doses could be generated from each allogeneic donor independent of recipient host health factors. Bulk NK cell production and storage could also dramatically decrease therapeutic cost and timing between recognized patient need and NK cell infusion.

An acknowledged limitation of CAR-NK cells to date has been the observed lack of robust *in vivo* expansion in non-engineered adoptive NK cell transfer trials (54). Cytokine (*e.g.*, IL-15, IL-21) NK cell stimulation has improved expansion and anti-tumor activity in preclinical models (112, 113). A phase 1 clinical trial is currently assessing the safety and potential efficacy of CD19CAR-NK cells co-expressing membrane-bound IL-15 in adults with relapsed/refractory B-cell malignancies (NCT03579927), but does not yet allow pediatric participation. Similar CD33CAR-NK strategies have demonstrated activity in preclinical AML models and have proven safe in patients, although durable responses have not been observed (114). Additional non-CAR cytokine-primed allogeneic NK cell immunotherapy trials are ongoing in adults and children with relapsed myelodysplastic syndrome or AML (NCT04024761, NCT03068819) (58, 115).

CONCLUSION

The enthusiasm for immunotherapy for children with high-risk leukemia is clearly warranted. However, appreciable therapeutic challenges remain, both in maximization of treatment efficacy and minimization of normal tissue toxicity. Future studies will continue to optimize ADC and BiTE immunotherapies (some in combination with chemotherapy) and identify the most optimal disease state and patient population(s) for treatment. For cellular therapies, the 'tunability' of engineered cell activity, cost of cell manufacturing, and time to patient infusion are of particular importance. Given the potential life-year gains in children with leukemia treated with immunotherapy, consideration of on-target/on-tumor activity and on-target/off-tumor bystander toxicity must also be carefully balanced. Long-term follow-up of treated patients with continued CAR T cell persistence will likely provide greater insight regarding potential effects upon fertility and embryologic toxicity.

The efficacy of leukemia-targeted immunotherapy in the absence of the common toxicities associated with cytotoxic chemotherapy is exciting. Even so, administration of bispecific T cell-engaging antibodies and engineered T cells are associated with risks of cytokine release syndrome (CRS) and immune effector cell neurotoxicity syndrome (ICANS), which can be life-threatening (116). T-cell activation, expansion, and resultant inflammation from these immunotherapies can manifest clinically as hypotension, tachycardia, hypoxia, and end-organ toxicity that require maximal supportive care, often in the intensive care unit setting when of high-grade (117). Though reversible in the majority of patients, CRS and ICANS benefit from early recognition and treatment or supportive care. Ongoing studies seek to identify associated biomarkers that may predict patients at particular risk for these toxicities (118). Interleukin-6 (IL-6) has been recognized as a critical mediator of systemic inflammatory toxicity resulting from both antibody-based and cellular immunotherapies. Severe immune hyperactivation can be successfully ameliorated in most patients with tociluzimab, an anti-IL-6 receptor monoclonal antibody now FDA-approved for treatment of CRS (119).

Ongoing and future studies will continue to optimize next-generation CAR T cell strategies for children with leukemia. Several groups have invented mechanisms for pharmacologic control of CAR expression or CAR-T activation (120–125), while others have designed infusible components to direct and control binding of the CAR to surface antigen targets (126, 127). CAR degradation, stimulated by small molecule blockade of proteasome-mediated degron cleavage, is another approach under current study (128). Ultimately, assessment of safety and toxicity will require bench-to-bedside translation and clinical trial testing, as animal models cannot perfectly predict human toxicity. The plasticity inherent in leukemias resistant to standard treatment regimens are likely drivers of both chemotherapeutic and immunotherapeutic resistance. Antigenic downregulation after immunotherapy has been identified as a major contributor to relapse. Strategies to either prevent or preemptively treat this immune escape are needed. For gene-modified therapies, there is a risk of insertional mutagenesis, a concern that has been reinforced now with identification of clonal CAR T cell expansion in two treated patients (129, 130). Nevertheless, the promise of cure in what was recently considered incurable leukemia is exhilarating and provides hope to stimulate continued scientific discovery.

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KEY POINTS

1. Immunotherapies have shown promising efficacy in treatment of children with highly chemotherapy-refractory leukemias.

2. Antibody-based therapeutics targeting leukemia-associated antigens appear safe and may overcome chemoresistance.

3. The success of cellular therapies, particularly engineered CAR-T and CAR-NK cells, has been transformative and has cured previously-incurable children.
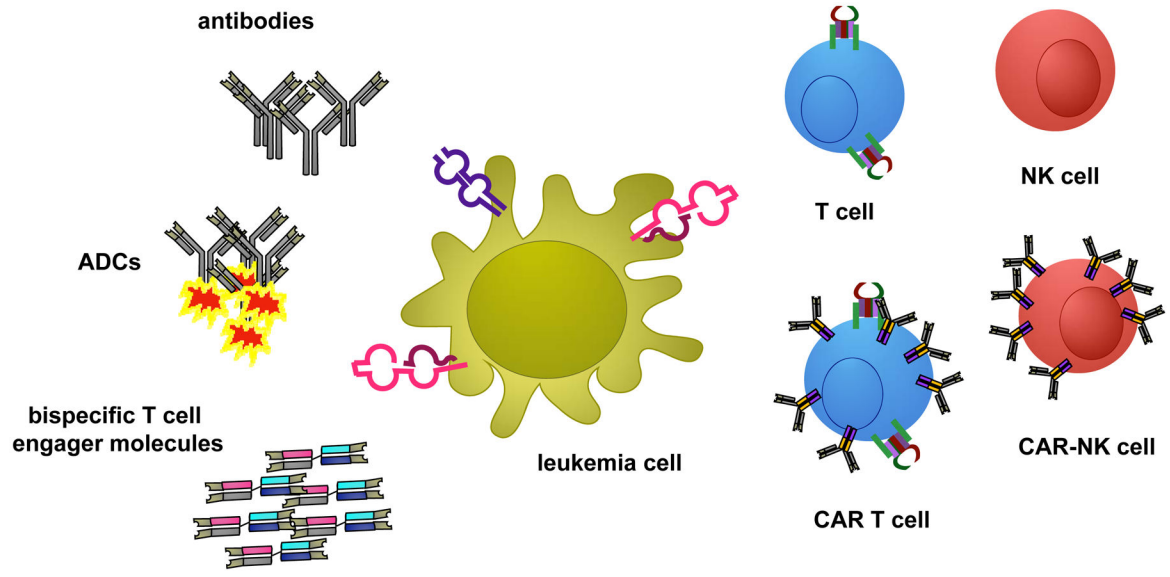
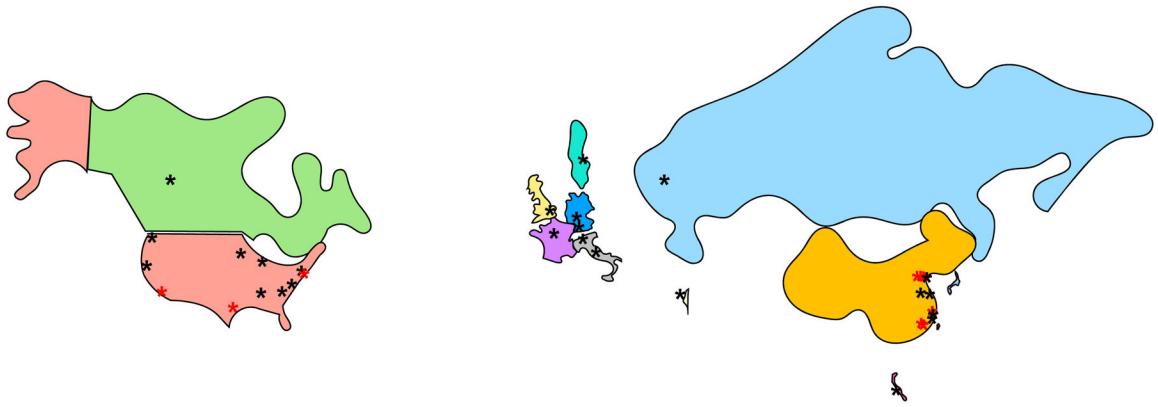**Figure 1. Schema of immunotherapy modalities for childhood leukemia.**

Figure 2. Geographic locations of current CAR T cell trials allowing pediatric patient participation.

Black = ALL trials, red = AML trials.

Table 1.

Current immunotherapy trials for patients with relapsed/refractory ALL.

Title	Registration Number	Eligible Ages	Sponsor
Study Evaluating KTE-C19 in Pediatric and Adolescent Subjects with Relapsed/Refractory B-Precursor Acute Lymphoblastic Leukemia (ZUMA-4)	NCT026525480	2–21 years	KITE/Gilead, Los Angeles, CA, USA
Transposon-Manipulated Allogeneic CARCIK-CD19 Cells in Pediatric and Adult Patients with r/r ALL Post HSCT (CARCIK)	NCT03389035	1–75 year	Fondazione Matilde Tettamanti Menotti De Marchi Onlus, Monza MI, Italy
Evaluation of CD19-specific CAR Engineered Autologous T-cells for Treatment of Relapsed/Refractory CD19+ Acute Lymphoblastic Leukemia	NCT03573700	21 years	St. Jude Children's Research Hospital, Memphis, TN, USA
CD19 T-CAR for Treatment of Children and Young Adults with r/r B-ALL	NCT03467256	3 months to 25 years	Federal Research Institute of Pediatric Hematology, Oncology and Immunology, Moscow, Russia
Study of UCART19 in Pediatric Patients with Relapsed/Refractory B Acute Lymphoblastic Leukemia (PALL)	NCT02808442	6 months to 17 years	Insitut de Recherches Internationales Servier, Paris, France
CAR-20/19-T cells in Pediatric Patients with Relapsed/Refractory B cell ALL (CAR-20/19-T)	NCT04049383	1–39.99 years	Medical College of Wisconsin, Milwaukee, WI, USA
Study of efficacy and safety of tisagenlecleucel in HR B-ALL EOC MRD Positive Patients (CASSIOPEIA)	NCT03876769	1–25 years	Novartis, Basel, Switzerland
Study of huCART19 for Very High-Risk (VHR) Subsets of Pediatric B-ALL	NCT03792622	1–29 years	University of Pennsylvania, Philadephia, PA, USA
T-cells Expressing Anti-CD19 CAR in Pediatric and Young Adults with B-Cell Malignancies	NCT02772198	1–50 years	Sheba Medical Center, Ramat Gan, Israel
Anti-CD19 CAR T cells in Pediatric Patients Affected by Relapsed/Refractory CD19+ALL and NHL	NCT03373071	6 months-25 years	Bambino Gesu Hospital and Research Institute, Rome, Italy
Anti-CD19, Dual Co-Stimulatory (4–1BB, CD3ς) Chimeric Antigen Receptor T-cells in Patients with relapsed/refractory aggressive lymphoma or acute lymphoblastic leukemia (ALL) (ACIT001/EXC002)	NCT03938987	2–70 years	University of Alberta, Edmonton, Alberta, Canada
CD22-Redirected Autologous T cells for ALL	NCT02650414	1–24 years	University of Pennsylvania, Philadephia, PA, USA
Administration of Autologous CAR-T CD19 Antigen with inducible Safety Switch in Patients with Relapsed/Refractory ALL	NCT03016377	3–70 years	UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA
MB-CART19.1 in Patients with R/R ALL	NCT03321123	2 months - 18 years	Shanghai Children's Medical Center, Shanghai, China
Pilot Study of Redirected Autologous T Cells Engineered to Contain Humanized Anti-CD19 In Patients with Relapsed or Refractory CD19+ Leukemia and Lymphoma Previously Treated with Cell Therapy	NCT02374333	1–24 years	University of Pennsylvania, Philadephia, PA, USA
Patient-Individualized Peptide Vaccination Based On Tumor-specific Mutations in Children and Young Adults with Primary/Relapsed ALL	NCT035559413	1–30 years	University Children's Hospital Tuebingen, Tuebingen, Germany
MB-CART19.1 r/r CD19+ B-cell Malignancies (BCM)	NCT03853616	1 year	Miltenyi Biotec GmbH, Bergisch Gladbach, Germany
Treatment of Patients with Relapsed or Refractory CD19+ Lymphoid Disease with T cells Expressing a Third-Generation CAR	NCT03676504	3 years	University Hospital Heidelberg, Heidelberg, Germany
CTL019 Ourt of Specification MAP for ALL or DLBCL Patients	NCT03601442		Novartis, Basel, Switzerland

Title	Registration Number	Eligible Ages	Sponsor
A Pediatric and Young Adult Trial of Genetically Modified T cells Directed Against CD19 for Relapsed/Refractory CD19+ Leukemia	NCT02028455	1–26 years	Seattle Children's Hospital, Seattle, WA, USA
Pilot Study of T-APCs Following CAR T cell Immunotherapy for CD19 Leukemia	NCT03186118	1–26 years	Seattle Children's Hospital, Seattle, WA, USA
CAR-T Therapy for Central Nervous System B-cell Acute Lymphocytic Leukemia	NCT03064269	10–60 years	Shanghai Unicar-Therapy Bio-medicine Technology Co., Ltd., Shanghai, China
CART-19 cells for R/R B-ALL (CCFRRBA)	NCT03391739	1–60 years	Fujian Medical University, Fuzhou, Fujian, China
CART-19 cells for MRD Positive CD19+ ALL (CCFMPCA)	NCT03027739	1–60 years	Fujian Medical University, Fuzhou, Fujian, China
CD19-specific CAR T cells with a fully human binding domain for CD19+ Leukemia or lymphoma	NCT03684889	1–28 years	Seattle Children's Hospital, Seattle, WA, USA
CARPALL: Immunotherapy with CD19 CAR T-cells for CD19+ Haematological Malignancies	NCT02443831	24 years	University College, London, England
CD19/22 CAR T cells (AUTO3) for the treatment of B cell ALL (AMELIA)	NCT03289455	1–24 years	Autolus Limited, White City, London, England
A feasibility and safety study of CD38 CAR-T cell immunotherapy for relapsed B-cell acute lymphoblastic leukemia after CD19 CAR-T adoptive cellular immunotherapy	NCT03754764	12–70 years	Chinese PLA General Hospital, Beijing, China
Safety and efficacy evaluation of IM19 CAR-T cells (IM19CAR-T)	NCT03142646	4–65 years	Beijing Immunochina Medical Science and Technology Co., Ltd., Beijing, China
CD19 CAR-T cells for Patients with Relapse and Refractory CD19+ B-ALL	NCT03671460	1 year	Tianjin Mycure Medical Technology Co., Ltd., Tianjin, China
Anti-CD19 CAR-T Therapy Combien with HSCT to Treat MRD+ B-cell Malignancies	NCT03366324	70 years	Wuhan Sian Medical Technology Co., Ltd., Wuhan, Hubei, China
CD19-CAR-T Cells in Patients with R/R B-ALL	NCT03574168	3–70 years	Bioceltech Therapeutics, Ltd., Beijing, China
CART-19 for Relapsed/refractory acute Lymphoblastic Leukemia (ALL)	NCT03544021	14–75 years	The Affiliated Hospital of the Chinese Academy of Military Medical Sciences, Shanghai, China
A study of C-CAR066 in subjects with r/r B cell Lymphoma who received CD19 CAR-T Therapy	NCT04036019	14–70 years	Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai, China
A clinical research of CD20-Targeted CAR-T in B Cell Malignancies	NCT02710149	14–75 years	Southwest Hospital China, Chongqing, China
A clinical research of CD22-Targeted CAR-T in B Cell Malignancies	NCT02935153	14–75 years	Southwest Hospital China, Chongqing, China
Anti-CD22 Chimeric Antigen Receptor (CAR)-Modified T cell Therapy for Relapsed Refractory B-cell Malignancies	NCT04007978	14–70 years	Wuhan Union Hospital, China, Jianghan, Wuhan, China
Anti-CD19 CAR-T Therapy Bridging to HSCT for CD19+ B-Cell Malignancies	NCT03366350	70 years	Wuhan Sian Medical Technology Co., Ltd., Wuhan, Hubei, China
Humanized CD19 CAR-T Cells with RS Suppression Technology for R/R CD19+ Acute Lymphoblastic Leukemia	NCT03275493	6–65 years	Shanghai Unicar-Therapy Bio-medicine Technology Co., Ltd., Shanghai, China
A feasibility and safety study of Universal Dual Specificity CD19 and CD20 or CD22 CAR-T Cell Immunotherapy for Relapsed or refractory Leukemia and Lymphoma	NCT03398967	12–70 years	Chinese PLA General Hospital, Beijing, China

Title	Registration Number	Eligible Ages	Sponsor
CD19-CAR Treatment for ALL	NCT03232619	6–70 years	Shanghai Bioray Laboratory Inc., Shanghai, China
CD19 Chimeric Antigen receptor (CAR)-modified T cell therapy in Treating Patients with B-cell Malignancies	NCT02965092	70 years	Wuhan Sian Medical Technology Co., Ltd., Whuan, Hubei, China
Phase I CD19/CD22 Chimeric Antigen Receptor T cells in Peds Recurrent/Refractory B cell Malignancies	NCT03241940	1–30 years	Stanford University, Palo Alto, CA, USA
Intravenous Autologou CD19-CAR-T Cells for R/R B-ALL	NCT03937544	13–65 years	National University of Malaysia, Bangi, Malaysia
Senl_1904A and Senl_1904B Chimeric Antigen Receptor (CAR) T-Cell in the Treatment of r/r Acute B Lymphocytic Leukemia	NCT03840317	3–65 years	Henei Senang Biotechnology Inc., Ltd., Shijiazhuang, Hebei, China
CART19 Cells Treatment of MRD of B cell Malignancies and then Auto-HSCT	NCT03685786	14–75 years	Shenzhen Second People's Hospital, Shenzhen, China
CAR-T Immunotherapy Targeting CD19-ALL	NCT04016129	6 months to 75 years	Shenzhen Second People's Hospital, Shenzhen, China
CD19-Directed CAR T cells Therapy in Relapsed/Refractory B cell Malignancy	NCT02537977	6–85 years	Shanghai Tongji Hospital, Tongji University School of Medicine
CAR-T Therapy Targeting to CD19 for R/R ALL	NCT03919240	No age posted	The First Affiliated Hospital of Soochow University
CD19-targeting, 3rd Generation CAR T Cells for Refractory B cells Malignancy	NCT03068416	100 years	Uppsala University, Uppsala, Sweden
A study of GC007F CAR-T Cell Immunotherapy for Relapsed or Refractory B-ALL	NCT03825718	2–70 yrs	Hebei Yanda Ludaopei Hospital, Yanjiao, Hebei, Chin
Humanized CD19 Chimeric Antigen Receptor (CAR)-Modified T cell Therapy in Treating Patients with B-cell Malignancies	NCT04008251	14–70 yrs	Wuhan Sian Medical Technology Co., Ltd., Wuhan, Hubei, China
Immunotherapy for High Risk/Relapsed CD19+ Acute Lymphoblastic Leukemia Using CAR T-cells to Target CD19 (ALLCAR19)	NCT02935257	16– 65 yrs	University College, London, England, UK
A Study of GC022 CAR-T Cell Immunotherapy for Relapsed or Refractory B-ALL	NCT03825731	2–70 yrs	Hebei Yanda Ludaopei Hospital, Yanjiao, Hebei, Chin
CD19/CD22-targeted Chimeric Antigen Recptor Engineered T cell (CART) in B-cell Acute Lymphblastic Leukemia	NCT03614858	6–65 yrs	Shanghai Unicar-Therapy Bio-medicine Technology Co., Ltd, Shanghai, China
Multi-CAR T Cell Therapy Targeting CD7-positive Malignancies	NCT04033302	6 months to 75 yrs	Shenzhen Geno-Immune Medical Institute, Shenzhen, China
A Clinical Research of CAR T cells Targeting CD19 Positive Malignant B-ell Derived Leukemia and Lymphoma	NCT02349698	4 –75 years	Southwest Hospital China, Chongqing, China
MT2017–45: CAR-T Cell Therapy for Heme Malignancies	NCT03642626	75 years	Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA
A Phase I/II Multiple Center Trial of 4SCAR19 Cells in the Treatment of Relapsed and Refractory B cell Malignancies	NCT03050190	6 months	Shenzhen Geno-Immune Medical Institute, Shenzhen, China
Production of Clinical-grade Anti-CD19 Chimeric antigen Receptor T cells for Refractory B-cell Malignancies	NCT03624686		National Taiwan University Hospital, Taipei, Taiwan
CD19/CD22 Chimeric Antigen Receptor (CAR) T cells in Children and Young Adults with Recurrent or Refractory CD19/CD22-expressing B cell Malignancies	NCT03448393	3–30 years	National Cancer Institute, Bethesda, MD
Autologous T cell expressing a Second Generation CAR for Traemtnet of T-Cell Malignancies Expressing CD5 Antigen (MAGENTA)	NCT03081910	75 yrs	Baylor College of Medicine, Houston, TX, USA

Title	Registration Number	Eligible Ages	Sponsor
Study of TBI-1501 for Relapsed or Refractory Acute Lymphblastic Leukemia (TBI-1501)	NCT03155191	16 years	Takara Bio, Inc., Kusatsu, Shiga Prefecture, Japan
Activated T-Cells Expressing 2nd or 3rd Generation CD19-Specific CAR, Advanced B-Cell NHL, ALL, and CLL (SAGAN)	NCT01853631	75 years	Baylor College of Medicine, Houston, TX, USA
CD19-hsCAR-T for Refractory/Relapsed CD19+ B-ALL Patients	NCT03902197	1–75 yrs	Xuanwu Hospital, Beijing, China
A Clinical Study Evaluating the Safety and Efficacy of BinD10 Treatment in Childhood R/R ALL and Lymphoma Subjects	NCT03265106	1–18 years	ShenZhen BinDeBio Ltd., Shenzhen, China
Safety and Efficacy Evaluation of CD19-UCART	NCT03229876	6–65 years	Shanghai Bioray Laboratory Inc., Shanghai, China
Treatment of Children CD19+ Leukemia and Non-Hodgkin Lymphoma With CD19-TriCAR-T/SILK Cell Therapy	NCT03910842	18 years	Timmune Biotech Inc., Hunan, China

Table 2.

Current immunotherapy trials for patients with relapsed/refractory AML.

Title	Registration Number	Eligible Ages	Sponsor
Evaluating QTc, PK, safety of gemtuzumab ozogamicin (GO) in patents with CD33+ R/R AML	NCT037227750	12 years	Pfizer, New York, NY, USA
Study of Adoptive Cellular Therapy Using Autologous T Cells Transduce with Lentivirus To Express A CD33 Specific Chimeric Antigen Receptor in Patients with Relapsed or Refractory CD33-positive Acute Myeloid Leukemia	NCT03126864	1–80 years	MD Anderson Cancer Center, Houston, TX, USA
Study of Anti-CD33 Chimeric Antigen Receptor-Expressing T Cells (CD33CART) in Children and Young Adults with Relapsed/Refractory Acute Myeloid Leukemia	NCT03971799	1–30 years	CIBMTR: National Cancer Institute, Bethesda, MD and Children's Hospital of Philadelphia, PA, USA
Study Evaluating the Safety, Tolerability, and Efficacy of FLT3 CAR-T AMG 553 in FLT3-Positive Relapsed/ Refractory AML	NCT03904069	12 years	Amgen, Thousand Oaks, CA, USA
Genetically Modified T-cell Immunotherapy in Treating Patients with Relapsed/Refractory Acute Myeloid Leukemia and Persistent/Recurrent Plastic Plasmacytoid Dendritic Cell Neoplasm	NCT02159495	12 years	City of Hope Medical Center, Duarte, CA, USA
CD123/CLL1 CAR-T Cells for R/R AML	NCT03631576	70 years	Fujian Medical University, Fuzhou, China
CAR-T cells Therapy in Relapsed/Refractory Acute Myeloid Leukemia (AML)	NCT03473457	6 months	Zhujiang Hospital, Guangzhou, China
Multiple CAR-T Cell Therapy Targeting AML	NCT04010877	6 months	Shenzhen Geno-Immune Medical Institute, Shenzhen, China
Safety and efficacy evaluation of IM23 CAR-T cells (IM23CAR-T)	NCT03585517	3–80 years	Beijing Immunochina Medical Science & Technology Co., Ltd., Beijing, China
Study Evaluating Safety and Efficacy of CAR-T cells targeting CD123 in Patients with Acute Myelocytic Leukemia	NCT03796390	2–65 years	Hebei Senang Biotechnology Inc., Ltd., Shijiazhuang, China
CART-123 for Relapsed/Refractory Acute Myelocytic Leukemia	NCT03556982	14–75 years	The Affiliated Hospital fo the Chinese Academy of Military Medical Sciences, Beijing, China
CAR-T Cells Therapy in Relapsed/Refractory Acute Myeloid Leukemia	NCT03473457	6 months	Guangzhou, China