

Key Clinical Trials and Real World Outcomes

<p>ELIANA registration trial¹</p>	<p>Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. <i>N Engl J Med.</i> 2018;378(5):439-448. doi:10.1056/NEJMoa1709866</p>	<p>https://pubmed.ncbi.nlm.nih.gov/29385370/</p>
<p>Humanized CAR T-cell therapy²</p>	<p>Myers RM, Li Y, Barz Leahy A, et al. Humanized CD19-Targeted Chimeric Antigen Receptor (CAR) T Cells in CAR-Naive and CAR-Exposed Children and Young Adults With Relapsed or Refractory Acute Lymphoblastic Leukemia. <i>J Clin Oncol.</i> 2021;39(27):3044-3055. doi:10.1200/JCO.20.03458</p>	<p>https://pubmed.ncbi.nlm.nih.gov/34156874/</p>
<p>Phase 2 ZUMA-3 trial^{3,4}</p>	<p>Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. <i>The Lancet.</i> 2021;398(10299):491-502. doi:10.1016/S0140-6736(21)01222-8</p> <p>Bouchkouj N, Lin X, Wang X, et al. FDA Approval Summary: Brexucabtagene Autoleucel for Treatment of Adults With Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia. <i>The Oncologist.</i> 2022;27(10):892-899. doi:10.1093/oncolo/oyac163</p>	<p>https://pubmed.ncbi.nlm.nih.gov/34097852/</p> <p>https://pubmed.ncbi.nlm.nih.gov/30309857/</p>
<p>Phase 1 ZUMA-4 trial⁵</p>	<p>Wayne AS, Huynh V, Hijiya N, et al. Three-year results from phase 1 of ZUMA-4: KTE-X19 in pediatric relapsed/refractory acute lymphoblastic leukemia. <i>Haematologica.</i> Published online October 20, 2022. doi:10.3324/haematol.2022.280678</p>	<p>Three-year results from phase 1 of ZUMA-4: KTE-X19 in pediatric relapsed/refractory acute lymphoblastic leukemia - PubMed (nih.gov)</p>
<p>CD19-directed CAR T with defined CD4+, CD8+ T-cell composition^{6,7}</p>	<p>Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. <i>Blood.</i> 2017;129(25):3322-3331. doi:10.1182/blood-2017-02-769208</p> <p>Shah NN, Highfill SL, Shalabi H, et al. CD4/CD8 T-Cell Selection Affects Chimeric Antigen Receptor (CAR) T-Cell Potency and Toxicity: Updated Results From a Phase I Anti-CD22 CAR T-Cell Trial. <i>J Clin Oncol.</i> 2020;38(17):1938-1950. doi:10.1200/JCO.19.03279</p>	<p>https://ashpublications.org/blood/article/129/25/3322/107614/Intent-to-treat-leukemia-remission-by-CD19-CAR-T</p> <p>https://pubmed.ncbi.nlm.nih.gov/32286905/</p>
<p>CIBMTR: Real-world outcomes⁸</p>	<p>Pasquini MC, Hu ZH, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. <i>Blood Adv.</i> 2020;4(21):5414-5424. doi:10.1182/bloodadvances.2020003092</p>	<p>https://pubmed.ncbi.nlm.nih.gov/33147337/</p>

CD19/22 CAR T-cells in CAYA with B-ALL ⁹	Shalabi H, Qin H, Su A, et al. CD19/22 CAR T cells in children and young adults with B-ALL: phase 1 results and development of a novel bicistronic CAR. <i>Blood</i> . 2022;140(5):451-463. doi:10.1182/blood.2022015795	CD19/22 CAR T cells in children and young adults with B-ALL: phase 1 results and development of a novel bicistronic CAR - PubMed (nih.gov)
CD22 CAR T-cells in CAYA with B-ALL ^{7,10}	<p>Shah NN, Highfill SL, Shalabi H, et al. CD4/CD8 T-Cell Selection Affects Chimeric Antigen Receptor (CAR) T-Cell Potency and Toxicity: Updated Results From a Phase I Anti-CD22 CAR T-Cell Trial. <i>J Clin Oncol</i>. 2020;38(17):1938-1950. doi:10.1200/JCO.19.03279</p> <p>Fry TJ, Shah NN, Orentas RJ, et al. CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. <i>Nat Med</i>. 2018;24(1):20-28. doi:10.1038/nm.4441</p>	<p>https://pubmed.ncbi.nlm.nih.gov/29155426/</p> <p>https://pubmed.ncbi.nlm.nih.gov/32286905/</p>
Current Best Practices using CAR T-cells in Children and young adults with B-ALL		
Dose Impact ¹¹	Stefanski H, Eaton A, Baggott C, et al. Higher doses of tisagenlecleucel associate with improved outcomes: a report from the pediatric real-world CAR consortium. <i>Blood Adv</i> . Published online August 8, 2022:bloodadvances.2022007246. doi:10.1182/bloodadvances.2022007246	https://pubmed.ncbi.nlm.nih.gov/35938863/
Optimal fludarabine exposure ^{12,13}	<p>Fabrizio VA, Boelens JJ, Mauguen A, et al. Optimal fludarabine lymphodepletion is associated with improved outcomes after CAR T-cell therapy. <i>Blood Adv</i>. 2022;6(7):1961-1968. doi:10.1182/bloodadvances.2021006418</p> <p>Dekker L, Calkoen FG, Jiang Y, et al. Fludarabine exposure predicts outcome after CD19 CAR T-cell therapy in children and young adults with acute leukemia. <i>Blood Adv</i>. 2022;6(7):1969-1976. doi:10.1182/bloodadvances.2021006700</p>	<p>https://pubmed.ncbi.nlm.nih.gov/34788386/</p> <p>https://pubmed.ncbi.nlm.nih.gov/35134115/</p>
Disease Burden ¹⁴⁻¹⁶	<p>Schultz LM, Baggott C, Prabhu S, et al. Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report. <i>J Clin Oncol</i>. Published online December 9, 2021:JCO.20.03585. doi:10.1200/JCO.20.03585</p> <p>Myers RM, Taraseviciute A, Steinberg SM, et al. Blinatumomab Nonresponse and High-Disease Burden Are Associated With Inferior Outcomes After CD19-CAR for B-ALL. <i>J Clin Oncol</i>. 2022;40(9):932-944. doi:10.1200/JCO.21.01405</p> <p>Ravich JW, Huang S, Zhou Y, et al. Impact of High Disease Burden on Survival in Pediatric Patients with B-ALL Treated with Tisagenlecleucel. <i>Transplant Cell Ther</i>. 2022;28(2):73.e1-73.e9. doi:10.1016/j.jtct.2021.11.019</p>	https://pubmed.ncbi.nlm.nih.gov/34882493/

Blinatumomab Non-response ¹⁵	Myers RM, Taraseviciute A, Steinberg SM, et al. Blinatumomab Nonresponse and High-Disease Burden Are Associated With Inferior Outcomes After CD19-CAR for B-ALL. <i>J Clin Oncol</i> . 2022;40(9):932-944. doi:10.1200/JCO.21.01405	https://pubmed.ncbi.nlm.nih.gov/34767461/
Cytogenetics ¹⁷	Leahy AB, Devine KJ, Li Y, et al. Impact of high-risk cytogenetics on outcomes for children and young adults receiving CD19-directed CAR T-cell therapy. <i>Blood</i> . 2022;139(14):2173-2185. doi:10.1182/blood.2021012727	https://pubmed.ncbi.nlm.nih.gov/34871373/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7252549/
Infections and Immune Reconstitution ^{18,19}	<p>Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. <i>Blood</i>. 2018;131(1):121-130. doi:10.1182/blood-2017-07-793760</p> <p>Hill JA, Seo SK. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. <i>Blood</i>. 2020;136(8):925-935. doi:10.1182/blood.2019004000</p>	https://pubmed.ncbi.nlm.nih.gov/29038338/ https://pubmed.ncbi.nlm.nih.gov/32582924/
Relapse Prevention and Management following CAR T-cells		
Role of MRD as Post-CAR T-cell predictor of Relapse ²⁰	Pulsipher MA, Han X, Maude SL, et al. Next-Generation Sequencing of Minimal Residual Disease for Predicting Relapse after Tisagenlecleucel in Children and Young Adults with Acute Lymphoblastic Leukemia. <i>Blood Cancer Discov</i> . 2022;3(1):66-81. doi:10.1158/2643-3230.BCD-21-0095	https://pubmed.ncbi.nlm.nih.gov/35019853/
Fate post-non CAR T-cell response and relapse ²¹	Schultz LM, Eaton A, Baggott C, et al. Outcomes After Nonresponse and Relapse Post-Tisagenlecleucel in Children, Adolescents, and Young Adults With B-Cell Acute Lymphoblastic Leukemia. <i>J Clin Oncol</i> . Published online September 15, 2022;JCO.22.01076. doi:10.1200/JCO.22.01076	https://pubmed.ncbi.nlm.nih.gov/36108252/
Pre-infusion factors impact relapse immunophenotype ²²	Lamble A, Myers RM, Taraseviciute A, et al. Preinfusion factors impacting relapse immunophenotype following CD19 CAR T cells. <i>Blood Adv</i> . Published online April 28, 2022;bloodadvances.2022007423. doi:10.1182/bloodadvances.2022007423	https://pubmed.ncbi.nlm.nih.gov/35482927/
Antigen Escape ²³	Majzner RG, Ramakrishna S, Yeom KW, et al. GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas. <i>Nature</i> . 2022;603(7903):934-941. doi:10.1038/s41586-022-04489-4	https://pubmed.ncbi.nlm.nih.gov/30135176/

CAR T-cell Associated Emergent Toxicities, Prevention, and Management

<p>CAR T-cell associated HLH-like toxicities^{24,25}</p>	<p>Lichtenstein DA, Schischlik F, Shao L, et al. Characterization of HLH-Like Manifestations as a CRS Variant in Patients Receiving CD22 CAR T-Cells. <i>Blood</i>. Published online September 15, 2021: blood.2021011898. doi:10.1182/blood.2021011898</p> <p>Hines MR, Keenan C, Maron Alfaro G, et al. Hemophagocytic lymphohistiocytosis-like toxicity (carHLH) after CD19-specific CAR T-cell therapy. <i>Br J Haematol</i>. 2021;194(4):701-707. doi:10.1111/bjh.17662</p>	<p>https://pubmed.ncbi.nlm.nih.gov/34525183/</p> <p>https://pubmed.ncbi.nlm.nih.gov/34263927/</p>
<p>Prophylaxis of severe toxicities</p> <p>Prophylactic anakinra²⁶</p> <p>Pre-emptive tocilizumab^{6,27}</p>	<p>Park JH, Romero FA, Taur Y, et al. Cytokine Release Syndrome Grade as a Predictive Marker for Infections in Patients With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia Treated With Chimeric Antigen Receptor T Cells. <i>Clin Infect Dis Off Publ Infect Dis Soc Am</i>. 2018;67(4):533-540. doi:10.1093/cid/ciy152</p> <p>Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. <i>Blood</i>. 2017;129(25):3322-3331. doi:10.1182/blood-2017-02-769208</p> <p>Kadauke S, Myers RM, Li Y, et al. Risk-Adapted Preemptive Tocilizumab to Prevent Severe Cytokine Release Syndrome After CTL019 for Pediatric B-Cell Acute Lymphoblastic Leukemia: A Prospective Clinical Trial. <i>J Clin Oncol</i>. 2021;39(8):920-930. doi:10.1200/JCO.20.02477</p>	<p>https://ashpublications.org/blood/article/138/Supplement%201/96/477545/A-Phase-II-Study-of-Prophylactic-Anakinra-to</p> <p>https://pubmed.ncbi.nlm.nih.gov/33417474/</p> <p>https://pubmed.ncbi.nlm.nih.gov/31697826/</p>
<p>Inflammatory Toxicities Grading and Practice Guidelines^{28,29, 30}</p>	<p>Maus MV, Alexander S, Bishop MR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events. <i>J Immunother Cancer</i>. 2020;8(2):e001511. doi:10.1136/jitc-2020-001511</p> <p>Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. <i>Biol Blood Marrow Transplant</i>. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758</p> <p>Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy — assessment and management of toxicities. <i>Nat Rev Clin Oncol</i>. 2018;15(1):47-62. doi:10.1038/nrclinonc.2017.148</p>	<p>https://pubmed.ncbi.nlm.nih.gov/33335028/</p> <p>https://pubmed.ncbi.nlm.nih.gov/30592986/</p> <p>https://pubmed.ncbi.nlm.nih.gov/28925994/</p>
<p>Special Considerations for CAR T-cells in Unique Populations</p>		
<p>Extramedullary disease^{31,32}</p>	<p>Fabrizio VA, Phillips CL, Lane A, et al. Tisagenlecleucel outcomes in relapsed/refractory extramedullary ALL: a Pediatric Real World CAR Consortium Report. <i>Blood Adv</i>.</p>	<p>https://pubmed.ncbi.nlm.nih.gov/</p>

	<p>2022;6(2):600-610. doi:10.1182/bloodadvances.2021005564</p> <p>Holland EM, Yates B, Ling A, et al. Characterization of extramedullary disease in B-ALL and response to CAR T-cell therapy. <i>Blood Adv.</i> 2022;6(7):2167-2182. doi:10.1182/bloodadvances.2021006035</p>	<p>.gov/34794180/</p> <p>Characterization of extramedullary disease in B-ALL and response to CAR T-cell therapy - PubMed (nih.gov)</p>
CAR T-cells for B-ALL with CNS involvement ^{33,34}	<p>Jacoby E, Ghorashian S, Vormoor B, et al. CD19 CAR T-cells for pediatric relapsed acute lymphoblastic leukemia with active CNS involvement: a retrospective international study. <i>Leukemia.</i> 2022;36(6):1525-1532. doi:10.1038/s41375-022-01546-9</p> <p>Leahy AB, Newman H, Li Y, et al. CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukaemia: a post-hoc analysis of pooled data from five clinical trials. <i>Lancet Haematol.</i> 2021;8(10):e711-e722. doi:10.1016/S2352-3026(21)00238-6</p>	<p>https://pubmed.ncbi.nlm.nih.gov/35468946/</p> <p>https://pubmed.ncbi.nlm.nih.gov/34560014/</p>
Infant B-ALL ^{35,36}	<p>Ghorashian S, Jacoby E, De Moerloose B, et al. Tisagenlecleucel therapy for relapsed or refractory B-cell acute lymphoblastic leukaemia in infants and children younger than 3 years of age at screening: an international, multicentre, retrospective cohort study. <i>Lancet Haematol.</i> 2022;9(10):e766-e775. doi:10.1016/S2352-3026(22)00225-3</p> <p>Moskop A, Pommert L, Baggott C, et al. Real-world use of tisagenlecleucel in infant acute lymphoblastic leukemia. <i>Blood Adv.</i> 2022;6(14):4251-4255. doi:10.1182/bloodadvances.2021006393</p>	<p>https://pubmed.ncbi.nlm.nih.gov/35580324/</p> <p>https://pubmed.ncbi.nlm.nih.gov/36084658/</p>
Trisomy 21 ³⁷	<p>Laetsch TW, Maude SL, Balduzzi A, et al. Tisagenlecleucel in pediatric and young adult patients with Down syndrome-associated relapsed/refractory acute lymphoblastic leukemia. <i>Leukemia.</i> 2022;36(6):1508-1515. doi:10.1038/s41375-022-01550-z</p>	<p>https://pubmed.ncbi.nlm.nih.gov/35422096/</p>
CAR T-cells: Biologic Correlatives Guiding Future Research		
CAR T cell correlatives and T cell profiling ^{38,39, 40, 41}	<p>Chen GM, Chen C, Das RK, et al. Integrative Bulk and Single-Cell Profiling of Premanufacture T-cell Populations Reveals Factors Mediating Long-Term Persistence of CAR T-cell Therapy. <i>Cancer Discov.</i> 2021;11(9):2186-2199. doi:10.1158/2159-8290.CD-20-1677</p> <p>Melenhorst JJ, Chen GM, Wang M, et al. Decade-long leukaemia remissions with persistence of CD4+ CAR T cells. <i>Nature.</i> 2022;602(7897):503-509. doi:10.1038/s41586-021-04390-6</p> <p>Singh N, Perazzelli J, Grupp SA, Barrett DM. Early memory</p>	<p>https://pubmed.ncbi.nlm.nih.gov/35110735/</p> <p>https://pubmed.ncbi.nlm.nih.gov/33820778/</p> <p>https://pubmed.ncbi.nlm.nih.gov/26738796/</p> <p>https://pubmed.ncbi.nlm.nih.gov/30630850/</p>

	<p>phenotypes drive T cell proliferation in patients with pediatric malignancies. <i>Sci Transl Med.</i> 2016;8(320). doi:10.1126/scitranslmed.aad5222</p> <p>Das RK, Vernau L, Grupp SA, Barrett DM. Naïve T-cell Deficits at Diagnosis and after Chemotherapy Impair Cell Therapy Potential in Pediatric Cancers. <i>Cancer Discov.</i> 2019;9(4):492-499. doi:10.1158/2159-8290.CD-18-1314</p>	
Expanding use of CAR T-cells in Pediatric Malignancies Beyond B-ALL		
CAR for T-cell malignancies ⁴²	Gomes-Silva D, Srinivasan M, Sharma S, et al. CD7-edited T cells expressing a CD7-specific CAR for the therapy of T-cell malignancies. <i>Blood.</i> 2017;130(3):285-296. doi:10.1182/blood-2017-01-761320	https://pubmed.ncbi.nlm.nih.gov/28539325/
CAR T-cells for Diffuse Midline Gliomas ²³	Majzner RG, Ramakrishna S, Yeom KW, et al. GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas. <i>Nature.</i> 2022;603(7903):934-941. doi:10.1038/s41586-022-04489-4	https://pubmed.ncbi.nlm.nih.gov/35130560/
CAR iNKT-cells for Neuroblastoma ⁴⁵	Heczey A, Courtney AN, Montalbano A, et al. Anti-GD2 CAR-NKT cells in patients with relapsed or refractory neuroblastoma: an interim analysis. <i>Nat Med.</i> 2020;26(11):1686-1690. doi:10.1038/s41591-020-1074-2	Anti-GD2 CAR-NKT cells in patients with relapsed or refractory neuroblastoma: an interim analysis - PubMed (nih.gov)
Other		
Outcomes using Tisagenlecleucel out of specification ⁴³	Rossoff J, Baggott C, Prabhu S, et al. Out-of-specification tisagenlecleucel does not compromise safety or efficacy in pediatric acute lymphoblastic leukemia. <i>Blood.</i> 2021;138(21):2138-2142. doi:10.1182/blood.2021012392	https://pubmed.ncbi.nlm.nih.gov/34499715/
Fertility and CAR T-cell therapy ⁴⁴	Ligon JA, Fry A, Maher JY, et al. Fertility and CAR T-cells: Current practice and future directions. <i>Transplant Cell Ther.</i> 2022;28(9):605.e1-605.e8. doi:10.1016/j.jtct.2022.06.002	Fertility and CAR T-cells: Current practice and future directions - PubMed (nih.gov)

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