**Approved and emerging CAR-Ts in acute lymphoblastic leukemia (ALL)**

Summary of the presentation from Mohamad MOHTY, MD, PhD

Clinical Hematology and Cellular Therapy Dpt. Sorbonne University, Saint-Antoine Hospital Paris, France

**Outcome of relapsed ALL:**

**Pediatric ALL:** 1992-2001 5-year pOS 0.45 ± 0.03, n=239 2002-2011 5-year pOS 0.58 :t 0.03, n=246 (Oskarsson et al. Haematologica. 2016 - DOI: [10.3324/haematol.2015.131680](https://doi.org/10.3324/haematol.2015.131680))

**Adult ALL:** Relapse during or after chemotherapy less than Relapse after transplantation (Gokbuget et al. Blood. 2012 - <https://doi.org/10.1182/blood-2011-09-377713>).

**CART-cells (Tisagenlecleucel; tisa-cel;Kymriah) in Pediatric B-cell ALL:**

ORR: 81%; CR: 60%; Cri: 21% (Maude SL. 2014 Oct 16;371(16):1507-17). [PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/25317870) | [CrossRef Full Text](https://doi.org/10.1056/NEJMoa1407222" \t "_blank) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=SL.+Maude&author=N.+Frey&author=PA.+Shaw&author=R.+Aplenc&author=DM.+Barrett&author=NJ.+Bunin+&publication_year=2014&title=Chimeric+antigen+receptor+T+cells+for+sustained+remissions+in+leukemia&journal=N+Engl+J+Med.&volume=371&pages=1507-17)

**CART cells in ALL: initial major published studies**

**CD28 containing CAR in Ped+YA – CR 61%.**

*Lee DW III, Stetler-Stevenson M, Yuan CM, Shah NN, Delbrook C, Yates B, et al. Long-term outcomes following CD19 CAR T cell therapy for B-ALL are superior in patients receiving a fludarabine/cyclophosphamide preparative regimen and post-CAR hematopoietic stem cell transplantation. Blood. (2016) 128:218. doi: 10.1182/blood.V128.22.218.218.* [*CrossRef Full Text*](https://doi.org/10.1182/blood.V128.22.218.218)*|*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=DW.+Lee&author=M.+Stetler-Stevenson&author=CM.+Yuan&author=NN.+Shah&author=C.+Delbrook&author=B.+Yates+&publication_year=2016&title=Long-term+outcomes+following+CD19+CAR+T+cell+therapy+for+B-ALL+are+superior+in+patients+receiving+a+fludarabine%2Fcyclophosphamide+preparative+regimen+and+post-CAR+hematopoietic+stem+cell+transplantation&journal=Blood.&volume=128&pages=218)

Lee DW, Kochenderfer JN, Stetler-Stevenson M, Cui YK, Delbrook C, Feldman SA, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *Lancet.* (2015) 385:517–28. doi: 10.1016/S0140-6736(14)61403-3. [PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/25319501) | [CrossRef Full Text](https://doi.org/10.1016/S0140-6736(14)61403-3" \t "_blank) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=DW.+Lee&author=JN.+Kochenderfer&author=M.+Stetler-Stevenson&author=YK.+Cui&author=C.+Delbrook&author=SA.+Feldman+&publication_year=2015&title=T+cells+expressing+CD19+chimeric+antigen+receptors+for+acute+lymphoblastic+leukaemia+in+children+and+young+adults%3A+a+phase+1+dose-escalation+trial&journal=Lancet.&volume=385&pages=517-28)

**1:1 CD4:CD8 in Ped+YA** **– CR 93%.**

*Gardner RA, Finney O, Annesley C, Brakke H, Summers C, Leger K, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. (2017) 129:3322–31. doi: 10.1182/blood-2017-02-769208.* [*PubMed Abstract*](https://pubmed.ncbi.nlm.nih.gov/28408462)*| [CrossRef Full Text](https://doi.org/10.1182/blood-2017-02-769208" \t "_blank) |*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=RA.+Gardner&author=O.+Finney&author=C.+Annesley&author=H.+Brakke&author=C.+Summers&author=K.+Leger+&publication_year=2017&title=Intent-to-treat+leukemia+remission+by+CD19+CAR+T+cells+of+defined+formulation+and+dose+in+children+and+young+adults&journal=Blood.&volume=129&pages=3322-31)

**Tisagenlecleucel in Ped+YA** **– CR 81%.**

*Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med. (2018) 378:439–48. doi: 10.1056/NEJMoa1709866.* [*PubMed Abstract*](https://pubmed.ncbi.nlm.nih.gov/29385370)*| [CrossRef Full Text](https://doi.org/10.1056/NEJMoa1709866" \t "_blank) |*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=SL.+Maude&author=TW.+Laetsch&author=J.+Buechner&author=S.+Rives&author=M.+Boyer&author=H.+Bittencourt+&publication_year=2018&title=Tisagenlecleucel+in+children+and+young+adults+with+B-cell+lymphoblastic+leukemia&journal=N+Engl+J+Med.&volume=378&pages=439-48)

**Tisagenlecleucel in Ped+YA – CR 89%.**

*Pasquini et al. (Clin Lymphoma Myeloma Leuk. (2019) 19:S267 (CIBMTR))\* Pasquini M, Hu ZH, Zhang Y, Grupp S, Hematti P, Jaglowski S, et al. Real world experience of tisagenlecleucel chimeric antigen receptor (CAR) T-cells targeting CD19 in patients with acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) using the center for international blood and marrow transplant research (CIBMTR) cellular therapy (CT) registry. Clin Lymphoma Myeloma Leuk.(2019) 19:S267. doi: 10.1016/j.clml.2019.07.190.* [*CrossRef Full Text*](https://doi.org/10.1016/j.clml.2019.07.190)*|*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=M.+Pasquini&author=ZH.+Hu&author=Y.+Zhang&author=S.+Grupp&author=P.+Hematti&author=S.+Jaglowski+&publication_year=2019&title=Real+world+experience+of+tisagenlecleucel+chimeric+antigen+receptor+(CAR)+T-cells+targeting+CD19+in+patients+with+acute+lymphoblastic+leukemia+(ALL)+and+diffuse+large+B-cell+lymphoma+(DLBCL)+using+the+center+for+international+blood+and+marrow+transplant+research+(CIBMTR)+cellular+therapy+(CT)+registry&journal=Clin+Lymphoma+Myeloma+Leuk.&volume=19&pages=S267)

**1:1 CD4:CD8 in Adults – CR 90%.**

*Turtle CJ, Hanafi LA, Berger C, Gooley TA, Cherian S, Hudecek M, et al. CD19 CAR–T cells of defined CD4+: CD8+ composition in adult B cell ALL patients. J Clin Invest. (2016) 126:2123–38. doi: 10.1172/JCI85309.* [*PubMed Abstract*](https://pubmed.ncbi.nlm.nih.gov/27111235)*| [CrossRef Full Text](https://doi.org/10.1172/JCI85309" \t "_blank) |*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=CJ.+Turtle&author=LA.+Hanafi&author=C.+Berger&author=TA.+Gooley&author=S.+Cherian&author=M.+Hudecek+&publication_year=2016&title=CD19+CAR–T+cells+of+defined+CD4+%3A+CD8++composition+in+adult+B+cell+ALL+patients&journal=J+Clin+Invest.&volume=126&pages=2123-38)

**1:1 CD4:CD8 in Adults – CRS 70%.**

*Hay KA, Hanafi LA, Li D, Gust J, Liles WC, Wurfel MM, et al. Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor–modified T-cell therapy. Blood. (2017) 130:2295–306. doi: 10.1182/blood-2017-06-793141.* [*PubMed Abstract*](https://pubmed.ncbi.nlm.nih.gov/28924019)*| [CrossRef Full Text](https://doi.org/10.1182/blood-2017-06-793141" \t "_blank) |*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=KA.+Hay&author=LA.+Hanafi&author=D.+Li&author=J.+Gust&author=WC.+Liles&author=MM.+Wurfel+&publication_year=2017&title=Kinetics+and+biomarkers+of+severe+cytokine+release+syndrome+after+CD19+chimeric+antigen+receptor–modified+T-cell+therapy&journal=Blood.&volume=130&pages=2295-306)

**MSKCAR-T in Adults – CR 83%.**

*Park JH, Riviere I, Gonen M, Wang X, Senechal B, Curran KJ, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. N Engl J Med. (2018) 378:449–59. doi: 10.1056/NEJMoa1709919.* [*PubMed Abstract*](https://pubmed.ncbi.nlm.nih.gov/29385376)*| [CrossRef Full Text](https://doi.org/10.1056/NEJMoa1709919" \t "_blank) |*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=JH.+Park&author=I.+Riviere&author=M.+Gonen&author=X.+Wang&author=B.+Senechal&author=KJ.+Curran+&publication_year=2018&title=Long-term+follow-up+of+CD19+CAR+therapy+in+acute+lymphoblastic+leukemia&journal=N+Engl+J+Med.&volume=378&pages=449-59)

**KTE-X19 1 :1 CD4:CD8 in Adults – CR 73%.**

*Shah N, Maatman T, Hari PN, Johnson B. Multi targeted CAR-T cell therapies for B-cell malignancies. Front Oncol. (2019) 9:146. doi: 10.3389/fonc.2019.00146.* [*PubMed Abstract*](https://pubmed.ncbi.nlm.nih.gov/30915277)*|*[*CrossRef Full Text*](https://doi.org/10.3389/fonc.2019.00146)*|*[*Google Scholar*](http://scholar.google.com/scholar_lookup?author=N.+Shah&author=T.+Maatman&author=PN.+Hari&author=B.+Johnson+&publication_year=2019&title=Multi+targeted+CAR-T+cell+therapies+for+B-cell+malignancies&journal=Front+Oncol.&volume=9&pages=146)

## See also: *Chimeric Antigen Receptor T-Cells in B-Acute Lymphoblastic Leukemia: State of the Art and Future Directions* *(REVIEW article in Front. Oncol., 26 August 2020 |*[*https://doi.org/10.3389/fonc.2020.01594*](https://doi.org/10.3389/fonc.2020.01594)*)*

**Real-World Outcomes for Pediatric and Young Adult Patients with Relapsed or Refractory (R/R) B-Cell Acute Lymphoblastic Leukemia (ALL) Treated with Tisagenlecleucel:**

*Update from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry:* [*Samuel John, et al. presented at ASH 21, Oral Session 905, Abstract 428.*](https://ash.confex.com/ash/2021/webprogram/Paper146393.html)

Efficacy outcomes of tisagenlecleucel in real-world were found to be similar to those observed in the [ELIANA](https://www.astctjournal.org/article/S1083-8791(18)31232-1/fulltext#relatedArticles) trial: OS @ 12months all pts 79.5% (ELIANA 77.1%); <18y 81.9%; ≥18y 73.8%. Efficacy median follow-up: 25.9 months; Patients received a median CAR+T cell dose of 1.9 x 106 cells/kg (N=534: 0.1-5.3); The median time from receipt of leukapheresis product at the manufacturing site to shipment was 26 days (N=522; IQR: 25-32).

**tisagenlecleucel (CTL019/Kymriah®) and axicabtagene ciloleucel (KTE-C19/Yescarta®):** The 2 constructs share identical recognition (FMC63-scFv) and signaling (CD3zita) domains, but the co-stimulatory domains differ: 4-1 BB for tisa-cel and CD28 for axi-cel.

**KTE-Xl9 for R/R B-ALL: phase 2 results of the single­arm, open-label, multicentre ZUMA-3 study:**

Between October 2018 and Oct 2019- Adults, PS: 0-1, >5% medullary blasts

KTE-X19: successfully manufactured: 92%; Median time: leuka to KTE-X19 release: 13d for US pts and 14.5 d for EU pts

Median follow-up: 16.4 m.

12/39 pts in CR/Cri were in ongoing remission

9 subsequent HSCT; 5 other anticancer therapies

12 (31%) relapsed; 1 died

6 mo-RFS and 12mo OS: consistent among groups: > 25% blasts, PH+ALL, previous HSCT, previous blina

SAE: 75%

Grade ≥3 cytopenia: 76% and were present on or after D30.

CRS: 89%, grade ≥3: 24%; median time to onset CRS: 5 days (3-7), median duration 7 .5 days (5-18).

Neurological events: 60%, grade􀀈 : 25%; median time to onset of

ICANS: 9 days (7-11), median duration 7 days (4-19).

Infections: grade≥ 3: 25%

Median time to peak CART cells on blood: 15 days (11-16).

An inverse relationship was observed between CAR T-cell expansion and BM blasts.

At 12 months in 10/12 ongoing responders with evaluable sample: all had recovered B cells and only 1 had detectable CART cells.

**This study showed that a single infusion of KTE-X19 could induce durable remission with manageable safety in heavily pre-treated adults with relapsed or refractory B-ALL.**

*Shah et aI. www.thelancet.com Published online June 4. 2021* [*https://doi.org/10.1016/S0140-6736(21)01222-8*](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01222-8/fulltext)

**Responses are not always durable:**

- Eliana trial: median FU of 24 m.: RFS was 62% with a plateau of the probability curves after 1 y

- Lower prelymphodepletion LDH concentration (HR, 1.38),

- Higher prelymphodepletion platelet count (HR, 0.74),

- Incorporation of fludarabine into the lymphodepletion regimen (HR, 0.25)

- HCT after CART-cell therapy (HR, 0.39) were associated with better EFS.

- Adults: median duration of response: 8-19 months with important variations in the proportion of

patients receiving consolidative HSCT in CR treatment (35-75%)

**Factors associated with duration of response:**

[Hay et al. Blood 2019](https://doi.org/10.1182/blood-2018-11-883710): phase 1/11 - 53 R/R B-ALL adults CD19 CAR-T cells

- Lower prelymphodepletion LDH concentration (HR, 1.38),

- Higher prelymphodepletion platelet count (HR, 0.74),

- Incorporation of fludarabine into the lymphodepletion regimen (HR, 0.25)

- HCT after CART-cell therapy (HR, 0.39) were associated with better EFS.

**Lymphodepletion:**

- More in vivo CART cells expansion and higher response rates: lymphodepletion with Flu-Cy versus no

Flu-Cy (Turtle et al. J Clin Inv. 2016)

- Association lymphodepletion intensity/ outcomes: OS > if Cy at 3 mg/m2 vs ≤1.5mg/m2 ([Curran et al.](https://doi.org/10.1182/blood.2020008394)

[Blood 2019](https://doi.org/10.1182/blood.2020008394))

**Outcomes in studies with adult patients with B-ALL who received allo-HCT after CAR T-cell therapy:**

[Shadman M. Blood Adv. 2019](https://pubmed.ncbi.nlm.nih.gov/31648329/): (FHCRC): N - 32 (19 ALL); MAC - 74%; CAR to aUoHCT- 72d

[Zhang Y. Br. J Haematol. 2020; 189: 146-152](https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.16339): N - 52; CAR to alloHCT- 50d; OS 1y 87.7%; EFS 1y 73%; relapse 1y 24.7%; TRM 1y 2.2%.

**Resistance to CAR-T cells therapy:**

CAR-T Cells

• Lack of expansion

• Lack of persistence

• Exhaustion

Tumor

• Cancer cells

* Loss of target antigen
* Resistance to immune killing

• Tumor microenvironment

- Impaired trafficking of T cells into the tumor

- Immune suppression:

o lmmunosuppressive cells (stroma, myeloid­derived suppressor cells, regulatory T cells)

o lmmunosuppressive cytokines (TGF/3, IL-10, IL-35)

*Jean Lemoine, et al. Overcoming Intrinsic Resistance of Cancer Cells to CAR T-Cell Killing.* [*Clin Cancer Res; 27(23) December 1, 2021*](https://watermark.silverchair.com/6298.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAA-owggPmBgkqhkiG9w0BBwagggPXMIID0wIBADCCA8wGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQM2TlayZyt-UlvypJbAgEQgIIDney_mu5zZssPGzmAQB4E_l_f7EBU93iTJXZXTMdmy0diBl3hM_cGw7yOUDUHP3IqLpMp8pa6hJGhbae-EFLqt78U3zM-SXoUqwf_6C-LFcvmtoJrO6XkgCyHqrp3mcZVMfyRtdKAeE0mE_UjvhGxDEr7j_PLM5tyGxGgdDDw0y0WTdU7lPrsO8QCtLs4GaJZmzB5R3zhAkCADKlNnyT2PEXrQ_jVON-2utK5jM-Yz10_DooFkvw1b77UbpewC_BtPiBQyTubAc0P7IrO-f7yPrz8FnKhPaXRHbx-li3Znm7gh5vk-VlCFX4_Bpt5dABjEZMur2iqyDYq5gr8__EU7LkdG1FBrXhLmtez07MSBJryAgfLX49hQhCbKbu9SUHkqg5HAnOawoii1dQ1y6QeynEKJKWfcWzI-Kzin6z8n1UStkPF4vt2ecos_Lb4dzRRtSd_ihtzheO6-IfXIJsJtNNKeNZLaX4sMW91x1HwOvCydWD9YAHDiDg5m2ucZLfg42W8n1JZltekOagLg4t9AcmfDM6dHwQd9UNJ_KIziTd81hCBK7VpxH8ypUKRLlwOm52d-51JWfbt7ZlGEDcwd1m8JJlv8qlDgZZrza-o7fnjxnAwuH-ppSks9vfFRASh2Q1TitfDV34IqOcxwbdGLcOWFFe1EmgeF6GsrF32OrelhUcFTy-Lfxdl7CN0tRP3JxHUeUxJNXJK8xcDcKraAfRXS3oiGJMGaW5rD0cZb52MfPC18zR0Z4LmZsQkN7nNeDKIvtDQ-j3sxBkPOizhJ8BdF4bGlRQE73Bq4xfet0qXxexBfRqz1xyuq6ZXy-9LXWQ6FDEIKIgUakS-_FtDzsWDsrcW7jLo08N55z4msPIiD_Mo98cSKruNX_5Gu3FNgZWjtj_oZgQe2GA8u6sbD1KZt78BTCkk3D4uyAI5VcBqYaW9ch1xZOS-M1zB6rR-CjwdVb_3mj2cBvvcM_ystExkm8DfshTSVTJPBkOcYg04p1N2gOtgvNCybnVvlo7wTD1nkjAkjCOYAPIiGIR95dW2fxctm4lH9FpyY7iJLSz04nQJ8AM-zSWlAxyatzQMB9RJbaOceYBT0T_NJFAyi4u7N9xTKp-PdiNSyBVxmWLHoajopdvr1JYoALoJpMA7YBkBh2Xy2Wd1QPGlb-TGIP2WFRbafqKx0rb0XifSInX-ezaiw9lKClnFZIcEEH-Y4Rt2TqUZtI9lgLt5e8k)

**Strategies to improve outcomes after CD19 CAR-T cell therapy:**

* Patient-/Disease-related: *•Referral timing •Debulking •Target Ag*
* Manufacturing: *• CAR design •Ex vivo expansion*
* Lymphodepletion: *•Type •Dose*
* CAR T Cell infusion: *•Cell dose •Repeated infusions*
* Combinatorial approaches: *•Checkpoint blockade •Others*

**CD19-positive relapses are associated with loss of CAR-T cell persistence**

*(Kevin A. Hay, et al.* Blood*(2019) 133 (15): 1652–1663.* [*https://doi.org/10.1182/blood-2018-11-883710*](https://doi.org/10.1182/blood-2018-11-883710)*)*

**Conclusions of MOHTY’s presentation**

CAR T-cell therapy for ALL: future directions

1. Improve duration of response - optimize CAR T-cell functionality

Better in vivo persistence

Decrease immunogenicity (human/humanized scFv)

Combination with immune checkpoint inhibitors

Prevent CD19-negative relapses (MLL-rearranged ALL++)

Multiantigen targeting (CD19 and CD22)

2. Positioning within the ALL treatment strategy/algorithm?

Consolidation in lieu of allo? bridge to allo? salvage after allo?

For salvage or MRD? How to sequence with blinatumomab, inotuzomab or combinations?

How to manage relapse after CAR-T cells?

3. Decrease toxicity:

Dose-adjustment/split-dosing according to B-cell burden?

CRS pre-emptive approaches?

Early intervention/guidelines (international guidelines)

Quality of life and cost effectiveness are yet to be established