**Approved and emerging CARTs in Non-Hodgkin’s Lymphoma**

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Number of CART-cell treated patients registered in the EBMT Registry

[EBMT Registry, October 2021](https://www.ebmt.org/ebmt-patient-registry)

Scholar-1 Study: Real World Outcomes in RR DLBCL ([Crump M, et al. Blood. 2017;130(16):1800](https://ashpublications.org/blood/article/130/16/1800/36474/Outcomes-in-refractory-diffuse-large-B-cell)):

Outcomes in patients with refractory / early relapse DLBCL were poor: 1-year and 2-year survival rates were 28% and 20%, respectively

Three Approved CD19 Constructs for Aggressive B Cell Lymphomas:

* KTE-C19 Axicabtagene ciloleucel (KITE) Gentransfer with Retrovirus: ZUMA-1 Trial. [Neelapu SS et al, NEJM 2017](https://www.nejm.org/doi/full/10.1056/nejmoa1707447).
* CTL-019 Tisagenlecleucel (Novartis) Gentransfer with Lentivirus: JULIET Trial. [Schuster SJ et al, NEJM 2019](https://www.nejm.org/doi/full/10.1056/nejmoa1804980).
* JCAR017 (CD4:CD8 = 1 :1) Lisocabtagene maraleucel (Juno Therapeutics/Celgene ) Gentransfer with Lentivirus: TRANSCEND Trial. [Abramson JS et al, Lancet 2020](https://www.thelancet.com/article/S0140-6736%2820%2931366-0/fulltext).

**Axicabtagene Ciloleucel in Patients with RR LBCL. Long­Term FU of ZUMA-1 (**[**Jacobson CA et al, ASH2021**](https://ash.confex.com/ash/2021/webprogram/Paper148078.html)**):**

* With ≥5 years of follow-up, the 5-year OS rate was 42.6% (95% Cl, 32.8-51.9) among patients treated with axi-cel
* The 5-year OS rate among complete responders was 64.4%(95% Cl, 50.8-75.1 ); the median survival time among complete responders was not reached (95% Cl, 63.4-NE); 37 of 59 CR patients (63%) are still alive at the 5-year data cutoff.
* Since the 4-year data cutoff, 1 death at Month 63 (CR) and 1 progressive disease at month 54 (PR) were observed.

**Tisagenlecleucel in Patients with RR LBCL. Long Term Results of JULIET (**[**Schuster SJ et al. Lancet Oncol 2021**](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2821%2900375-2/fulltext)**):**

* Best overall response:
* Complete response 45 (39%)
* Partial response 16 (14%)
* Stable response 15 (13%)
* Progressive disease 30 (26%)
* ORR 61 (53%)
* Median time to first response: 29 days

**Lisocabtagene Maraleucel in Patients with RR LBCL. Long Term Results of TRANSCEND (**[**Abramson JS et al, Lancet 2020**](https://www.thelancet.com/article/S0140-6736%2820%2931366-0/fulltext)**.)**

* Best ORR: 73%, best CR: 53%, 12 months DOR 55%.
* Probability (95%) of PFS at 2 years 40.6% (34.0-47.2%), median (95%) follow-up, 23.9 months (23.7-24.0).
* Probability (95%) of OS at 2 years 50.5% (44.1-56.5%), median (95%) follow-up, 29.3 months (26.2-30.4).

Improving Survival of RR LBCL with the Use of CART Cell Constructs ([Neelapu SS et al, Blood Adv 2021](https://ashpublications.org/bloodadvances/article/5/20/4149/476779/Comparison-of-2-year-outcomes-with-CAR-T-cells)):

* Propensity analysis confirmed substantially higher ORR and a 73% reduction in risk for death with axi-cel vs standard salvage regimens.
* This 2-year analysis indicates that axi-cel is associated with durable clinical benefit for patients with refractory LBCL.

**Real Life Experience with Axi-cel in RR LBCL (**[**Jacobson CA et al, ASCO 2021**](https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7552)**):**

Overall response rate (ORR): 73%; Patients with refractory disease at the time of axi-cel infusion had an ORR of 68%.

Complete remission rate (CR): 55%;

Median PFS was 7.75 months (95% Cl 6.14-11.07)

**Real Life Experience with Tisagenlecleucel in RR LBCL (**[**Landsburg D et al, ASH2021**](https://ash.confex.com/ash/2021/webprogram/Paper146397.html)**)**

* Response rates were similar between JULIET-ineligible patients (ORR: 55.7%, CR: 41.6%) and the overall CIBMTR population (57.4%, 42.4%); both reflect the rates seen in JULIET (53.0%, 39.1%),
* Month 12 PFS rates were similar between JULIET-ineligible patients (34.2%) and the overall CIBMTR population (33.1%); both reflect that seen in JULIET (34.6%).

Real Life Experience with Axi-Cel / Tisa-Cel in LBCL in SP (Kwon M, et al, submitted)

**The Importance of Real-World Evidence. Identification of Prognostic Factors for Long Term Outcome:**

[Nastoupil Let al, JCO 2020](https://ascopubs.org/doi/full/10.1200/JCO.19.02104): Kaplan-Meier curves for ECOG PS ≥ 2 and elevated LDH are shown as common covariates that affect PFS and OS ([Figs 3A-3D](https://ascopubs.org/doi/full/10.1200/JCO.19.02104)),

[Neelapu SS et al, Blood 2020](https://ashpublications.org/blood/article/135/23/2106/452706/Outcomes-of-older-patients-in-ZUMA-1-a-pivotal): PFS in patients ≥65 and <65 years of age ([Figure](https://ashpublications.org/DownloadFile/DownloadImage.aspx?image=https://ash.silverchair-cdn.com/ash/content_public/journal/blood/135/23/10.1182_blood.2019004162/2/bloodbld2019004162f1.png?Expires=1648664162&Signature=hckB-XggJYdclkyQ90R7eV7t8tCS1d032UbP1kctX5-YgJFVGzO7PZ7iQIYFPvnxOql0PvLUs5MlsujIsADJT9esAhd~ExfWe93ctcSVzVwdLhSv04aH~kx6Wo1F-hCGsn5obtvN~mBxkFFJmm4dOZKVpKn1jSWcm9YhfpboCpqWw9yOi0UUIfKEXZ7q8vhSVPMzXU5E1RDwVN3xwTen8TfT9gImgcMVlo6sxSps4cSEtrcpK4tV0z~FzgrMgmpL1u56t2gprGCal9siuJMxUiVNJZA8X5ZBCYVGSxPZFoL30yawzDcmdfpABwi6UvZckFIGmsRacuAEgiamkO-vvQ__&Key-Pair-Id=APKAIE5G5CRDK6RD3PGA&sec=9733456&ar=452706&xsltPath=~/UI/app/XSLT&imagename=&siteId=1000001)),

[Nastoupil Let al, JCO 2020](https://ascopubs.org/doi/full/10.1200/JCO.19.02104), [Jacobson CA et al JCO 2020](https://ascopubs.org/doi/full/10.1200/JCO.19.02103): In comparing a panel of immunomodulatory markers on CAR+/− T cells at time points before and after therapy, identified differences in T-cell activation markers (Ki67, ICOS) were identified that were associated with response. In this small subset, CAR+/− T cells were more highly activated and proliferative in responders).

[Vercellino L et al, Blood Adv 2020](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7686887/): Factors: ≥2 extranodal sites and TMlV >80 ml

[Kuhnl A et al, Blood Adv 2022](https://ashpublications.org/bloodadvances/article/6/1/321/477468/Early-FDG-PET-response-predicts-CAR-T-failure-in): The results indicate that early FDG-PET response using Deauville criteria may predict the risk of CAR-T failure and be used to guide post–CAR-T management.

**Moving CART Cells to 2nd Line Tx for Primary Refractory and Early Relapsed DLBCL. ZUMA-7 (**[**Locke F et al, ASH2021**](https://ash.confex.com/ash/2021/webprogram/Paper148039.html)**):**

Primary EFS Endpoint: Axi-cel is Superior to SOC: HR 0.398 (95% Cl, 0.308-0.514); P<0.0001

Median EFS (95% Cl) 8.3 (4.5-15.8) vs. 2.0 (1.6-2.8) months,

24-mo EFS Rate (95% Cl) 40.5% (33.2-47.7) 16.3% (11.1-22.2).

**Moving CART Cells to 2nd Line Tx for Primary Refractory and Early Relapsed DLBCL. TRANSFORM ([Kamdar Met al, ASH2021](https://ash.confex.com/ash/2021/webprogram/Paper147913.html)):**

* SOC median EFS: 2.3 months, 95% Cl, 2.2-4.3
* Liso-cel median EFS: 10.1 months, 95% Cl, 6.1-NR

**ZUMA-12. Testing the Role of Axicabtagene as First Line Therapy in Patients with High Risk DLBCL (**[**Neelapu SS et al. ASH 2021. Abstract 739**](https://ash.confex.com/ash/2021/webprogram/Paper148009.html)**):**

With 15.9 months of median follow-up, responses were durable as medians for DOR, EFS, and PFS were not yet reached and over 70% of patients remained in response at data cutoff.

**We Do Have New Indications!!**

**ZUMA-2 (**[**Wang M et al, NEJM 2020**](https://www.nejm.org/doi/full/10.1056/NEJMoa1914347)**):**

KTE-X19 induced durable remissions in a majority of patients with relapsed or refractory mantle-cell lymphoma.

[**Brexucabtagene Autoleucel**](https://ash.confex.com/ash/2021/webprogram/Paper153277.html) **in RR MCL:** analysis reveals nearly identical response and toxicity rates compared to those reported on ZUMA-2. These results corroborate the efficacy of brexu-cel in a population of older adults with high-risk disease features.

[**ZUMA-5**](https://www.thelancet.com/article/S1470-2045%2821%2900591-X/fulltext) for RR FL: high rates of durable responses and had a manageable safety profile in patients with relapsed or refractory indolent non-Hodgkin lymphoma.

[**ELARA**](https://ash.confex.com/ash/2021/webprogram/Paper145025.html) for RR FL: tisagenlecleucel produced high ORR and CRR and was associated with durable response and promising 12-mo PFS in pts with r/r FL and 2+ prior lines of therapy.

**CONCLUSIONS**

* The introduction of CART cell therapy has revolutionized th of patients with B-Cell NHL
* Excellent results in phase II pivotal prospective clinical trials
* Real world data in both EU and US replicate results of PCT
* Identification of prognostic factors
* New indications (diseases, early stages) will be coming soon