NEXT-GENERATION CAR-T CELL THERAPY FOR HIGH-RISK LBCL AND R/R DLBCL

INSIGHTS & ADVANCES IN TECHNOLOGY

Breaking down next generation CAR-T cell therapy
2025 A year in review

Springer Health+ IME

KEY CHALLENGES

Current CAR-T cell therapies face logistical, manufacturing and clinical integration challenges

Complex and long manufacturing **process (>14 days)**, with a long **vein-to-vein time (>27 days).**[1-2]

Treatment delays and worsening of patient condition necessitating bridging therapy.

High relapse rates (around 50%) and low persistence due to prolonged T-cell expansion and preferential proliferation of differentiated T-cells rather than more persistent naïve and stem cell memory T cells, as well as antigen escape (loss of expression on cancer cells).[3]

High risk for toxicity: CRS: any grade 42–93%; grade 3 or worse 2–20% and ICANS: any grade 21–64%; grade 3 or worse 10–28%[4-6]

NEXT-GENERATION CAR-T CELL THERAPY STRATEGIES

Improved manufacturing, efficacy, and durability

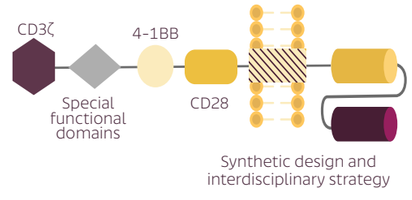
Rapid manufacturing platforms (<2 days) that enhance in-vivo T-cell expansion and preserve T-cell quality for greater persistence, and longer time to side effects.[6]

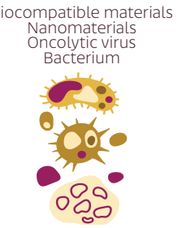
Decentralized manufacturing and automated manufacturing using a fresh, more viable product, to reduce vein-to-vein time (approximately 7 days and 13–15 days, respectively).[7]

Dual antigen targeting to overcome antigen loss and improve T-cell persistence and efficacy.

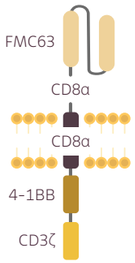
Costimulatory domains to boost T-cell performance.

Allogeneic CAR-T cells, using donor cells for a quicker, off-the-shelf product





2025 CLINICAL DATA



Rapcabtagene autoleucel (phase 2)

CD-19-directed CAR-T therapy using a rapid manufacturing platform (T-Charge™)

Setting: R/R DLBCL[7]

Dose: 12.5 x 10^6 CAR-T cells per kg

Response CR: 65%; ORR: 88%

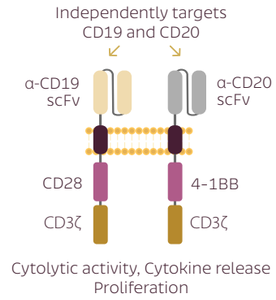
Toxicity	CRS	ICANS
Any grade	44%	8%
Grade ≥3	6%	5%
Median time to onset	8 days	13 days
Median duration	4 days	19 days

Setting: First-line, high-risk LBCL[9]

Dose: 12.5 x 10^6 CAR-T cells per kg

Response CR: 74%; ORR: 89%

Toxicity	CRS	ICANS
Any grade	49%	8%
Grade ≥3	0%	2%
Median time to onset	11 days	15 days
Median duration	6 days	17 days



Cytolytic activity, Cytokine release Proliferation

KITE-753 (phase 1)[10]

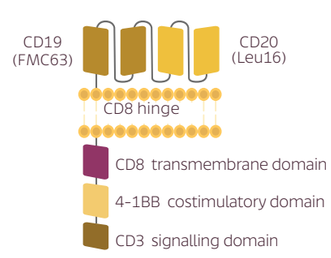
Independent CD19/CD20-directed CAR-T therapy with dual costimulation of CD28 and 4-1BB, produced using a rapid manufacturing platform

Setting: R/R LBCL

Dose: 0.2 x 10^6 CAR-T cells per kg

Response CR: 70%; ORR: 80%

Toxicity	CRS	ICANS
Any grade	53%	11%
Grade ≥3	0%	0%
Median time to onset	6 days	10 days
Median duration	5 days	2 days



Zamtocabtagene autoleucel (phase 2; DALY 2-EU study)[8]

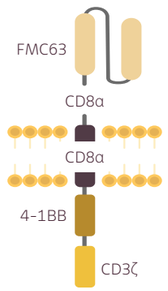
Tandem CD19/CD20-directed CAR-T therapy with dual costimulation of CD28 and 4-1BB, produced using a fully automated system (CliniMACS Prodigy®) and administered as a fresh product

Setting: R/R LBCL versus R-GemOX

Dose: 2.5 x 10^6 CAR-T cells per kg

Response CR: 54%; ORR: 72%

Toxicity	CRS	ICANS
Any grade	78%	11%
Grade ≥3	5%	1%
Median time to onset	2 days	10 days
Median duration	6 days	5 days



GLPG5101 (phase 1/2; ATALANTA-1)[11]

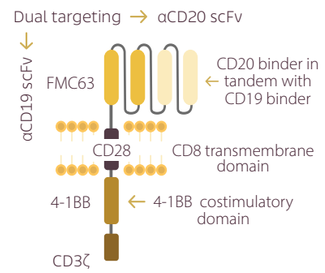
CD-19-directed CAR-T therapy, using a closed, fully automated decentralized manufacturing system and administered as a fresh product

Setting: R/R DLBCL

Dose: 50 x 10^6, 110 x 10^6, 250 x 10^6 CAR-T cells

Response CR: 54%; ORR: 69%

Toxicity	CRS	ICANS
Any grade	43%	20%
Grade ≥3	2%	2%
Median time to onset	7 days	12 days
Median duration	3 days	2 days



Prizlo-cel (JNJ-90014496; phase 1b)[12]

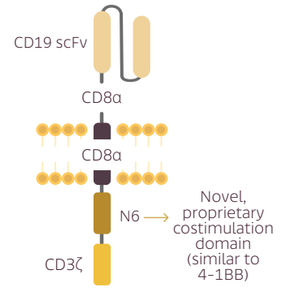
Tandem CD19/CD20-directed CAR-T therapy with dual costimulation of CD28 and 4-1BB

Setting: R/R LBCL

Dose: 2.0 x 10^6 CAR-T cells per kg, 150 x 10^6 CAR-T cells, 75 x 10^6 CAR-T cells

Response CR: 75%; ORR: 91%

Toxicity	CRS	ICANS
Any grade	80%	16%
Grade ≥3	4%	8%
Median time to onset	3 days	3 days
Median duration	5 days	17 days



Azer-cel combined with interleukin (IL)-2 (phase 1/1b)[13]

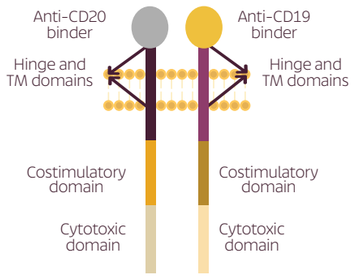
Allogeneic CD19-directed CAR-T therapy combined with subcutaneous IL-2 for exogenous armoring

Setting: R/R LBCL; relapsed after autologous CAR-T therapy

Dose: 500 x10^6 CAR-T cells plus IL-2 at 1 x 10^6 IU

Response CR: 44%; ORR: 81%

Toxicity	CRS	ICANS
Any grade	72%	17%
Grade ≥3	0%	11%
Median time to onset	3 days	5 days
Median duration	2 days	1 day



Lucar-G39D (phase 1)[14]

Allogeneic, independent CD19/CD20-directed gamma delta CAR-T cell therapy with dual costimulation

Setting: R/R B-cell non-Hodgkin Lymphoma

Dose: 30 x 10^6, 100 x 10^6, 200 x 10^6, 400 x 10^6, 600 x 10^6, 800 x 10^6 CAR-T cells

Response CR: 38%; ORR: 75%

Toxicity	CRS	ICANS
Any grade	56%	0%
Grade ≥3	13%	0%
Median time to onset	3 days	
Median duration	5 days	

KEY INSIGHTS

Next-generation CAR-T cells show the potential to:

- Offer rapid treatment
- Simplify production and widen applicability
- Provide a better-quality product
- Enhance T-cell persistence and improve response rates, without significantly increasing toxicity
- Delay time to onset of serious side effects facilitating outpatient treatment

ABBREVIATIONS

R/R: Relapsed/Refractory; DLBCL: diffuse large B-cell lymphoma; CR: complete response rate; ORR: objective/overall response rate; CRS: cytokine-release syndrome; ICANS: immune effector-cell neurotoxicity syndrome

REFERENCES

1. Shah M, Krull A, Odonnell L, de Lima MJ, Bezerra E. Promises and challenges of a decentralized CAR T-cell manufacturing model. Front Transplant. 2023 Sep 5;2:1238535.
2. Locke FL, Siddiqi T, Jacobson CA, et al. Impact of vein-to-vein time in patients with R/R LBCL treated with axicabtagene ciloleucel. Blood Adv. 2025 Jun 10;9(11):2663–2676.
3. Bock TJ, Colonne CK, Fiorenza S, et al. Outcome correlates of approved CD19–targeted CAR T cells for large B cell lymphoma. Nat Rev Clin Oncol. 2025 Apr;22(4): 241–263
4. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022; 386: 640–654.
5. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019; 380: 45–56.
6. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020; 396: 839–852.
7. Westin J, Chavez J, Schuster SJ, et al. Rapcabtagene autoleucel (YTB323) for patients with first line high-risk large B-cell lymphoma: phase II interim results. Abstract presented at: ASH Annual Meeting 2025; December 5, 2025; Orlando, FL, USA.
8. Borchmann P, Van Meerten T, Bories P, et al. Zamtocabtagene autoleucel, a tandem CD20–CD19 directed CAR-T cell therapy as second-line treatment for relapsed/refractory large B–cell lymphoma: primary analysis of the randomized, pivotal DALY 2-EU study. Abstract presented at: ASH Annual Meeting 2025; December 7, 2025; Orlando, FL, USA.
9. Kwon M, Riedell P, Flinn IW, et al. Rapcabtagene autoleucel (YTB323) in patients with relapsed/refractory diffuse large B-cell lymphoma: a phase II trial clinical update. Abstract presented at: EHA2025 Congress; June 13, 2025; Virtual and Milan, Italy.
10. Dahiya S, Ulrickson M, Yared J, et al. A phase 1 study of KITE-753 or KITE-363 in patients with relapsed/refractory B-cell lymphoma: initial safety and preimmary efficacy of KITE-753 and updated results of KITE-363. Abstract presented at: ASH Annual Meeting 2025; December 6, 2025; Orlando, FL, USA.
11. Vermaat J, Anguille S, Kuipers M, et al. Low rates of high-grade toxicities with GLPC5101, a fresh, stem-like, early memory phenotype anti-CD19 CAR T-cell therapy in patients with non-Hodgkin lymphoma in the ATALANTA-1 study. Abstract presented at: EHA2025 Congress; June 15, 2025; Virtual and Milan, Italy.
12. Patel K, Rhodes J, Mountjoy L, et al. A global phase 1b study of JNJ-90014496, a CD19/CD20 bi-specific chimeric antigen receptor CAR T-cell therapy, in patients with relapsed/refractory large B-cell lymphoma. Abstract presented at: EHA2025 Congress; June 13, 2025; Virtual and Milan, Italy.
13. Gupta S, Waller E, Reshef R, et al. Azer-cel, an allogeneic CD19 CAR T, in combination with low-dose interleuken-2 demonstrates clinical activity in patients with large B-cell lymphoma who relapsed after autologous CAR T. Abstract presented at: ASH Annual Meeting 2025; December 6, 2025,Orlando, FL, USA
14. Yu J, Cao L, Li L, et al. A phase 1 study of LUCAR-G39D: a novel anti-CD20/CD19 dual-CAR allogeneic γd T cells in adults with relapsed/refractory B-Cell non-Hodgkin lymphoma. Abstract presented at: ASH Annual Meeting 2025; December 6, 2025, Orlando, FL, USA.