# When the CARs crash... What next? A review of relapsed/refractory treatment options for Diffuse Large B-cell Lymphoma

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# Objectives

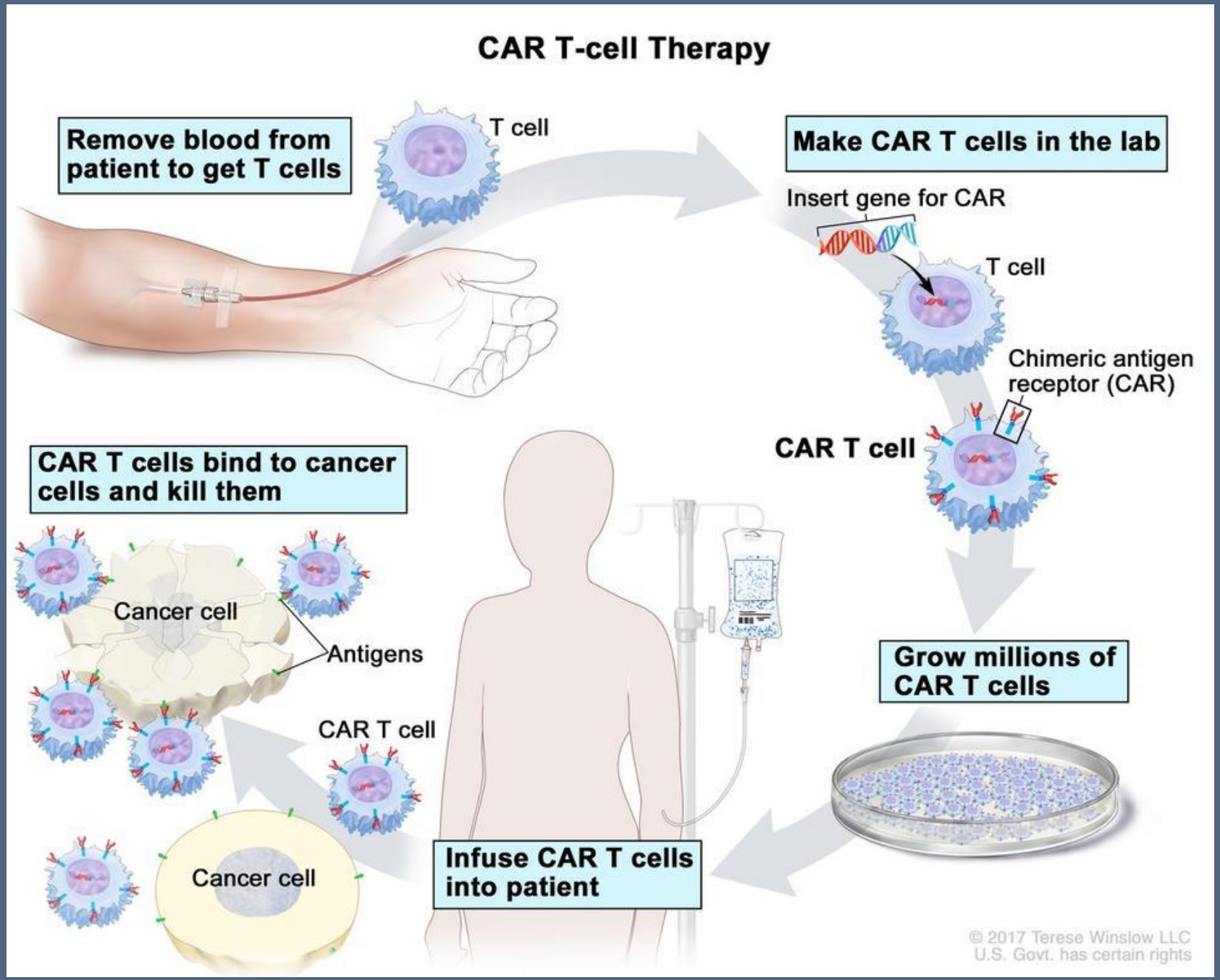
- Review current treatment strategies for relapsed and/or refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)
- Examine the application of Chimeric Antigen Receptor T-cell therapy (CAR T) in the treatment of Diffuse Large B-Cell Lymphoma (DLBCL)
- Assess the success and failure rates of CAR T therapy, and explore treatment alternatives in the context of CAR T failure
- Explore innovative treatment options for relapsed or refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)

# Abbreviations

- AlloHCT – allogeneic hematopoietic cell transplant
- AutoHCT – autologous hematopoietic cell transplant
- CMR – complete metabolic response
- CR – complete response
- DOR – duration of response
- ECOG – Eastern Cooperative Oncology Group
- HGBL – high grade B-cell lymphoma
- IPI – International Prognostic Index
- MCL – Mantle cell lymphoma
- MDSC – myeloid derived suppressor cells
- NHL – Non-Hodgkin lymphoma
- ORR – overall response rate
- OS – overall survival
- PMBL – primary mediastinal B-cell lymphoma
- PS – performance status
- RF – risk factors
- scFV – single chain fragment variables
- TAM – tumor associated macrophages
- Tregs – T regulatory cells

# Treatment Approach to Relapsed/Refractory Disease

- Refractory or relapsed < 12 months
  - Candidate for CAR T
    - Proceed to bridging therapy as needed + CAR T
  - Not a candidate
    - Consider clinical trial, second-line therapy, palliative radiation, supportive care
- Relapsed > 12 months
  - Candidate for transplant
    - Second-line therapy
      - Complete response: autoHCT, clinical trial, alloHCT
      - Partial response: CAR T, autoHCT, clinical trial, alloHCT
      - No response: third-line therapy, clinical trial, palliative radiation, supportive care
  - Not a candidate for transplant
    - Consider clinical trial, second-line therapy, palliative radiation, supportive care


CAR T-cell Therapy
Remove blood from patient to get T cells
T cell
Make CAR T cells in the lab
Insert gene for CAR
T cell
Chimeric antigen receptor (CAR)
CAR T cell
CAR T cells bind to cancer cells and kill them
Cancer cell
Antigens
CAR T cell
Cancer cell
Infuse CAR T cells into patient
Grow millions of CAR T cells
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# Chimeric Antigen Receptor Therapy (CAR-T) in DLBCL

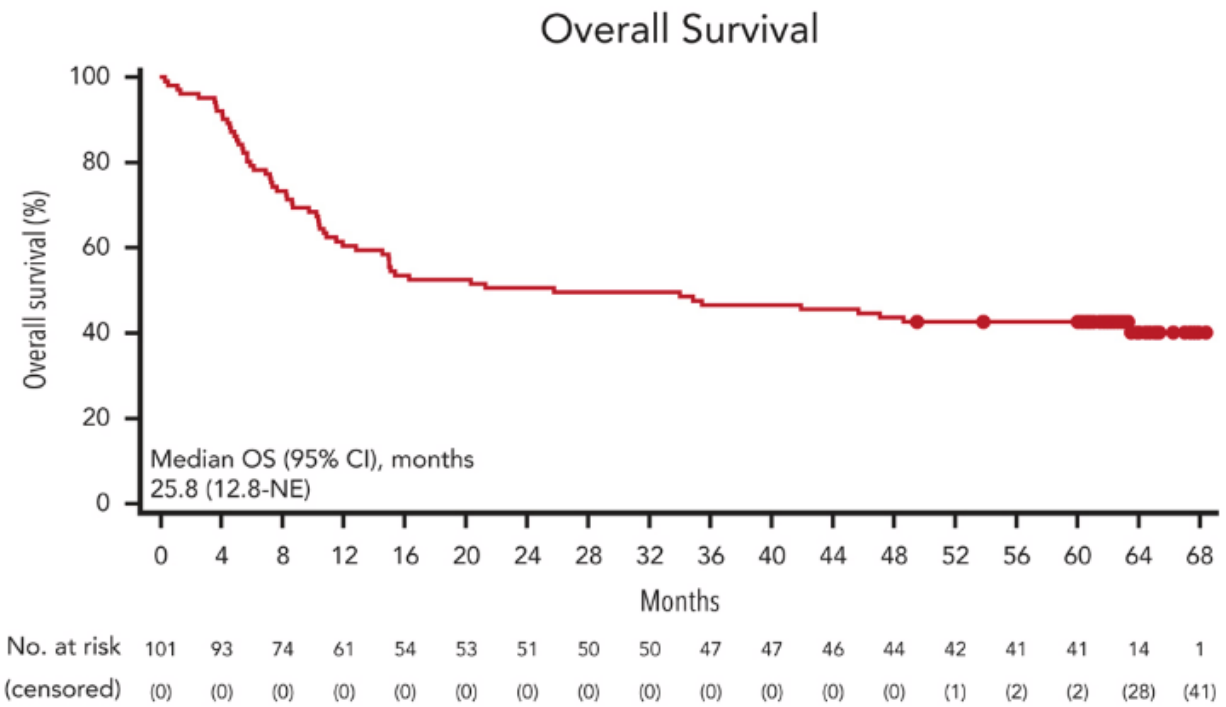
- Axicabtagene ciloleucel (axi-cel)
  - Use in refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy; treatment of R/R DLBCL in adults after ≥ 2 lines of systemic therapy
- Lisocabtagene maraleucel (liso-cel)
  - Use in refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy; treatment of R/R DLBCL in adults after ≥ 2 lines of systemic therapy
- Tisagenlecleucel (tisa-cel)
  - Use to treat R/R DLBCL in adults after ≥ 2 lines of systemic therapy

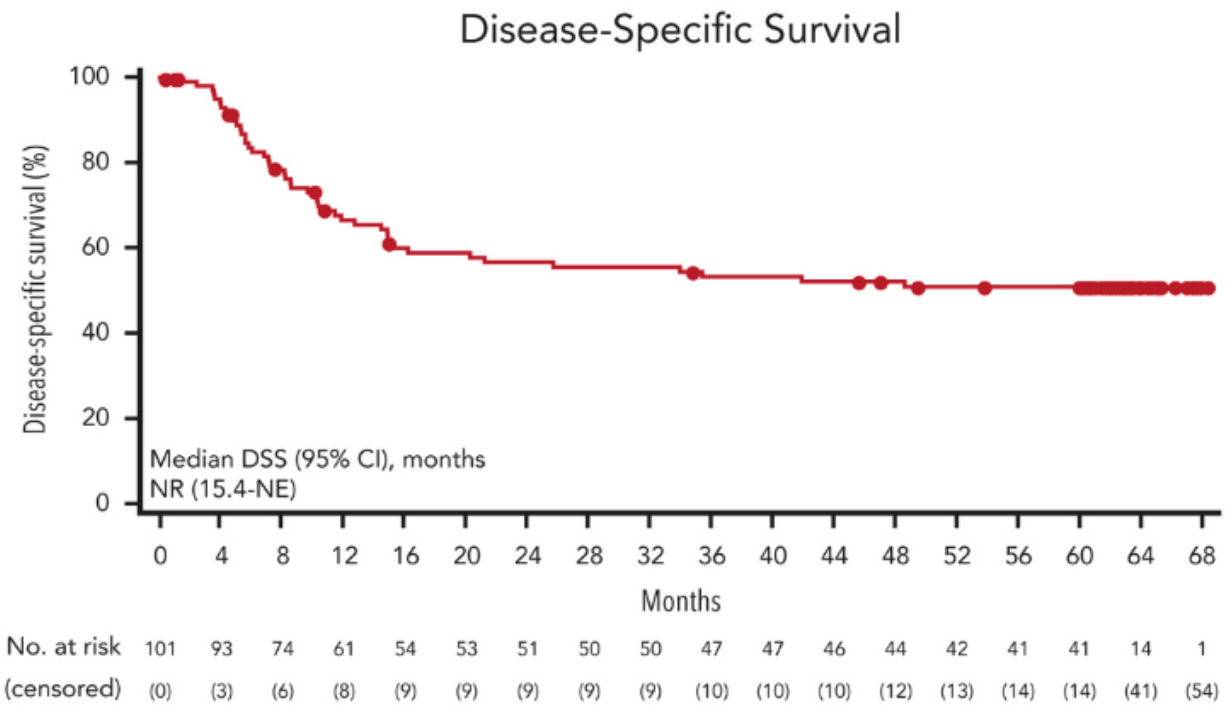
# CAR T Response Rates

| | Axi-cel [1] (ZUMA-1 5-year f/u) | Liso-cel [2] (TRANSCEND 2-year f/u) | Tisa-cel [3] (JULIET) |
|---|---|---|---|
| Number of patients | 101 | 92 | 115 |
| ORR | 83% | 73% | 53% |
| CR | 58% | 53% | 39% |
| Median DOR | 11.1 months | 23.1 months | Not reached |
| Median duration of CR | 62.2 months | 26.1 months | Not reached |

1) Neelapu, et al. Blood (2023) 141 (19): 2307–2315.
2) Abramson, et al. Blood (2024) 143 (5): 404–416.
3) Schuster, et al. Lancet Oncol 2021; 22: 1403–15.

# Long-Term Survival With Axi-Cel in Patients With Refractory Large B-Cell Lymphoma




Neelapu, et al. Blood (2023) 141 (19): 2307–2315.

# CAR T Response Rates

- Rate of long-term cure is approximately 40%[1]
- Factors associated with longer duration of response[2]
  - Deep initial response
  - Lower baseline tumor volume
  - Peak circulating CAR T-cell levels
  - Lymphodepleting chemotherapy

1) Abramson. Blood (2022) 140 (24): 2527–2529.
2) Cappell and Kochenderfer. Nat Rev Clin Oncol. 2023 Jun;20(6):359-371.

# CAR T Failure

- Tisa-cel (JULIET trial): ~60% of patients had progressed at 6 months
- Axi-cel (ZUMA 1) and liso-cel (TRANSCEND) trials showed ~50% of patients had progressed at 6 months
- Data confirmed in real-world series

1) Neelapu, et al. Blood (2023) 141 (19): 2307–2315.
2) Schuster, et al. Lancet Oncol 2021; 22: 1403–15.

# Predictive Factors for Early CAR T-cell Failure

- Cohort study conducted in France between Jun 2018 - Jan 2020
- Purpose: to evaluate characteristics or risk factors (RF) that could predict early progression or relapse within the first month after CAR T-cell therapy
- Included 116 patients at the time of decision to use CAR T-cell therapy and at the time of treatment
  - Axicabtagene ciloleucel, n = 49
  - Tisagenlecleucel, n = 67
- Median follow-up, 8.2 months
- Results:
  - 55 patients failed CAR T-cell therapy; 49% were early progressors
  - Estimated 12-month PFS 47.2% (95% CI 38 – 58.6)
  - Estimated 12-month OS 67% (95% CI 57 – 79)

- Identified RFs for early progression at time of decision to use CAR T and time of treatment with CAR T were:
  - Extranodal sites ≥ 2
  - Elevated lactate dehydrogenase
  - High total metabolic tumor volume

Vercellino L, et al. Blood Adv. 2020. 24; 4(22):5607-5615.

# Barriers to CAR T-cell Therapy

- Access Concerns
  - Timely product manufacturing and collection of quality T-cells
  - Timely infusion of CAR T-cells
    - Product failure because of poor cell growth
    - Disease progression or other complications before cell infusion
  - CAR T-cell activation and expansion
    - Disease burden can affect T-cell expansion and increase risk of toxicity
  - Access to CAR T-cell therapy
    - Limited manufacturing programs
    - Increased need for cellular therapy infusion centers with the capacity and capability to administer these products successfully and safely
- Disease Relapse and Limited Remission
- Toxicity Concerns

Shah NN, et al. Nat Rev Clin Oncol. 2019; 16(6):372-385
Liu Z, et al. Exp Hematol Oncol. 2024; 13(1):22.

# Proposed Mechanisms of CAR T-cell Failure

| Mechanisms of Resistance | | Strategies to Overcome Resistance | |
|---|---|---|---|
| T-cell related factors: | •Lack of multi-cytokine producing cells<br>•Poor quality of donor T-cells<br>•Anti-CD19 scFv derived murine cells<br>•Inappropriate percentage of CD4+ and CD8+ CAR T-cells<br>•Nature of co-stimulatory domain | T-cell related factors: | •Early referral and leukapheresis to improve quality of T-cells<br>•Optimization of CAR T-cell constructs<br>•Use of fully human or humanized scFv instead of murine derived ones reduce associated immunogenicity and toxicity |
| Tumor cell related factors: | •Heterogeneity<br>•Antigen loss and/or down regulation<br>•Lineage switching<br>•Gene mutations | Tumor cell related factors: | •CRISPR/Cas-9 engineered universal CAR T-cells<br>•Multi-targeted CAR T-cells targeting multiple antigens on tumors to overcome antigen loss or downregulation |
| Tumor microenvironment related factors: | •Immunosuppressive chemokine signals and chemotaxis<br>•Treg cells, MDSCs, TAMs<br>•Metabolic fuel deprivation | Tumor microenvironment related factors: | •Armored CAR T-cells to secrete cytokines or other therapeutic agents to enhance activity in the tumor microenvironment<br>•Use of combination therapy – CARs plus other agents, such as checkpoint inhibitors of chemotherapy to augment and enhance the immune response |

Shah NN, et al. Nat Rev Clin Oncol. 2019; 16(6):372-385
Liu Z, et al. Exp Hematol Oncol. 2024; 13(1):22.

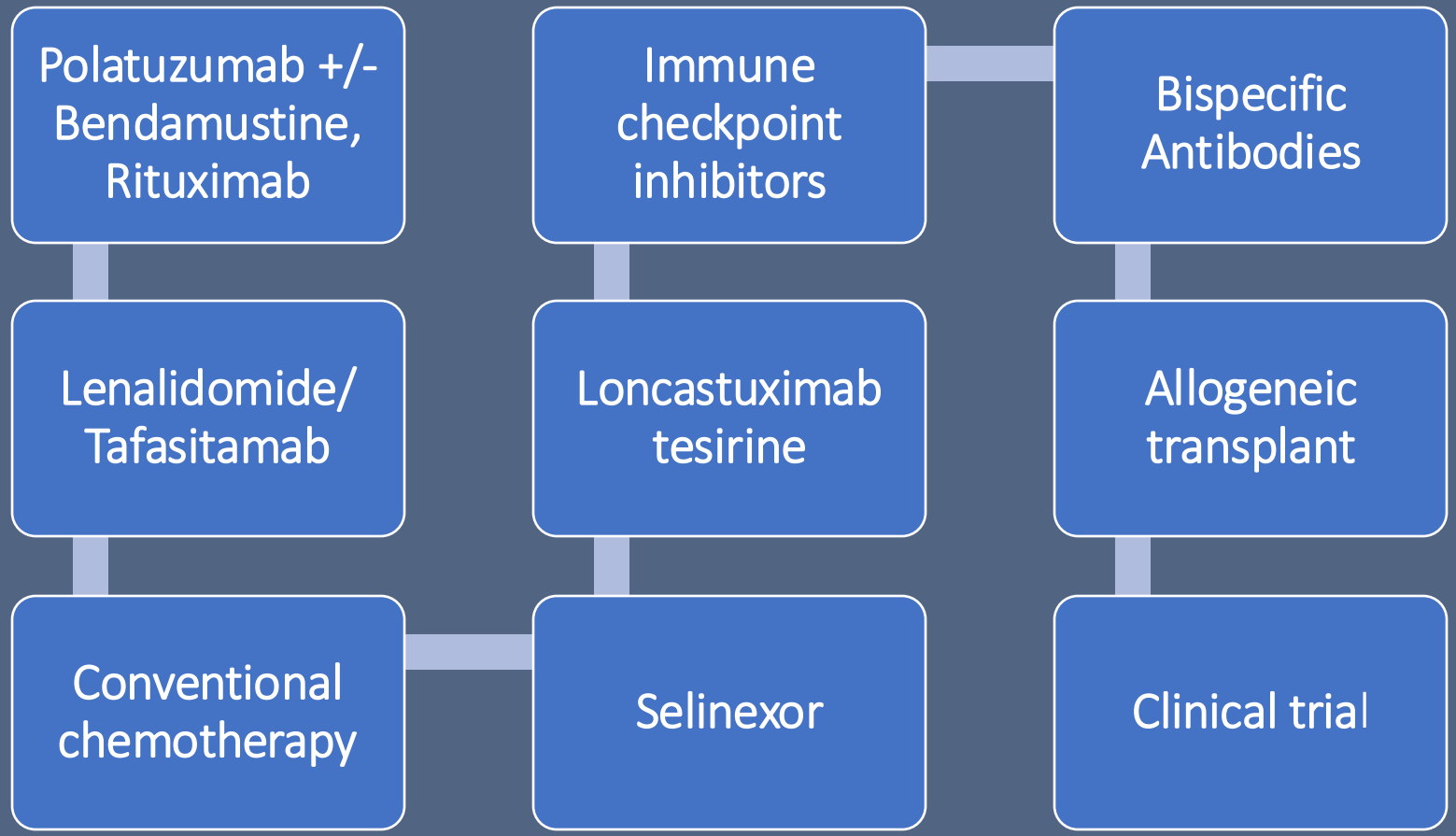
# Outcomes After CAR T Failure

- Median OS from the first post-CAR-T treatment was 8 months[2]
- Polatuzumab, standard chemotherapy, and lenalidomide-based treatments were the most common approaches after CAR-T.[2]
- Factors associated with poor OS[2]
  - pre-CAR-T bulky disease
  - lack of response to CAR-T
  - age >65 years
  - elevated LDH at post-CAR-T treatment
  - The presence of ≥2 of these factors was associated with inferior OS compared to ≤1 (56% vs. 19%)


1) Di Blasi, et al. Blood. 2022 Dec 15;140(24):2584-2593.
2) Leukemia. 2023 January ; 37(1): 154–163.

# Treatment Options After CAR T Failure

- No current standard of care




Tomas, et al. Leukemia. 2023 January ; 37(1): 154–163.

# Treatment Options After CAR T Failure: Bispecific Antibodies

- CD3-CD20 Bispecific Antibodies

| | Epcoritamab[1] | Glofitamab[2] |
|---|---|---|
| Previous CAR T-cell therapy in Phase 1/2 study | 38.9% | 33% |
| Refractory to previous CAR T-cell therapy in Phase 1/2 study | 75.4% | 30% |
| CR in patients who previously received CAR T | 34.4% | 35% |
| CR in all enrolled patients | 38.9% | 39% |


1) Thieblemont, et al. J Clin Oncol. 2023 Apr 20;41(12):2238-2247.
2) Dickinson, et al. N Engl J Med 2022;387:2220-2231

# Treatment Options After CAR T Failure: Glofitamab + Polatuzumab

- Polatuzumab vedotin: CD79b-targeted antibody-drug conjugate

| | **Glofitamab + Polatuzumab[1]** |
|---|---|
| Previous CAR T-cell therapy in Phase 1/2 study | 24.3% |
| CMR in patients who previously received CAR T | 44.4% |
| CMR in all enrolled patients | 56% |

1) Hutchinges, et al. Blood (2023) 142 (Supplement 1): 4460.

# Treatment Options After CAR T Failure: ViPOR

- Venetoclax, ibrutinib, prednisone, obinutuzumab, lenalidomide

| ViPOR | Results |
|---|---|
| Previous CAR T-cell therapy in Phase 1b/2 study | 33% |
| ORR in all DLBCL patients | 54% |
| CR in all DLBCL patients | 38% |
| 2-year PFS in all DLBCL patients | 34% |
| 2-year PFS and OS in prior CAR T patients ★ | 30% |
| ORR | 45% |
| CR | 20% |

Melani C, et al. N Engl J Med. 2024 Jun 20;390(23):2143-2155.

# Future Considerations

16 clinical trials in R/R DLBCL evaluating bispecifics in combination with other agents


| Study Title | NCT Number | Interventions | Status |
|---|---|---|---|
| CAR T followed by Bispecific Antibodies | NCT04889716 | Mosunetuzumab (Cohort 1) or obinutuzumab and glofitamab (Cohort 2) when given after CAR (genetically modified) T cells | Recruiting |
| Clinical Study With Blinatumomab in Patients With Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL) | NCT01741792 | Safety and efficacy of the bispecific T-cell engager blinatumomab in R/R DLBCL | Completed with results |
| Treatment by a Bispecific CD3xCD20 Antibody for Relapse/Refractory Lymphomas After CAR T-cells Therapy | NCT04703686 | Phase 2 trial of glofitamab (with obinutuzumab lead-in) in R/R DLBCL patients at least 1 month after CAR infusion<br>Cohort 1: DLBCL<br>Cohort 2: PMBL, MCL, transformed indolent patients | Active, not recruiting |
| Study Investigating the Safety and Efficacy of Blinatumomab in Combination With Pembrolizumab in Adults With Relapsed or Refractory DLBCL | NCT03340766 | To determine the maximum tolerated dose (MTD) of blinatumomab in combination with pembrolizumab | Completed with results |
| A Study of AZD0486 in Subjects With Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma | NCT04594642 | Phase 1 trial of CD19 x CD3 T-cell engaging bispecific antibody, in subjects with relapsed or refractory B-cell non-Hodgkin lymphoma (B-NHL) who have received 2 or more prior lines of therapy | Recruiting |
| A Phase 2 Study of Firi-cel in Patients With Relapsed/Refractory Large B-cell Lymphoma | NCT05972720 | firicabtagene autoleucel (firi-cel), a CD22-directed autologous Chimeric Antigen Receptor (CAR) T-cell therapy | Recruiting |
| CD30biAb-AATC for CD30+ Malignancies | NCT05544968 | CD30 antibody conjugated to a CD3 antibody that is preloaded onto a patient's own T-cells, generating a CD30 bispecific antibody-armed, anti-CD3-activated, autologous T-cells (CD30 biAb-AATC) | Not yet recruiting |
| Loncastuximab Tesirine and Mosunetuzumab for the Treatment of Relapsed or Refractory DLBCL | NCT05672251 | Phase 2 trial Evaluate the safety and tolerability of loncastuximab tesirine plus mosunetuzumab | Recruiting |

Search for: Relapsed/Refractory Diffuse Large B-Cell Lymphoma, bispecific antibody | List Results | ClinicalTrials.gov. Accessed: October 31, 2024

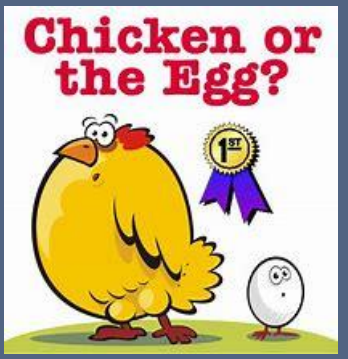
# Future Considerations

16 clinical trials in R/R DLBCL evaluating bispecifics in combination with other agents


| Study Title | NCT Number | Interventions | Status |
|---|---|---|---|
| Testing Drug Treatments After CAR T-cell Therapy in Patients With Relapsed/Refractory DLBCL | NCT05633615 | Phase 2 trial comparing PFS in R/R LBCL or FL after CD19 CAR T-cell therapy randomized to either<br>Arm 1: mosunetuzumab consolidation to no consolidation<br>Arm 2: polatuzumab vedotin consolidation to no consolidation<br>Arm 3: mosunetuzumab + polatuzumab vedotin to no consolidation | Recruiting |
| Testing the Combination of Anti-cancer Drugs Mosunetuzumab, Polatuzumab Vedotin, and Lenalidomide for the Treatment of R/R DLBCL | NCT06015880 | Phase 1 trial to determine the safety and tolerability of mosunetuzumab + polatuzumab vedotin + lenalidomide | Recruiting |
| Mosunetuzumab in Combination With Platinum-Based Salvage Chemotherapy in Autologous Stem Cell Transplant-Eligible Patients With Relapsed/Refractory Aggressive B Cell Lymphoma | NCT05464329 | Phase Ib study with expansion cohorts evaluating the safety and efficacy of mosunetuzumab in combination with platinum-based salvage chemotherapy in autologous stem Cell transplant-eligible patients | Recruiting |
| Mosunetuzumab Consolidation Therapy After autoSCT in r/r Aggressive B Cell Lymphoma | NCT05412290 | Phase 1 study examines the feasibility and safety of mosunetuzumab after autologous stem cell transplant | Recruiting |
| Modified Immune Cells (CD19/CD20 CAR-T Cells) in Treating Patients With Recurrent or Refractory B-Cell Lymphoma or Chronic Lymphocytic Leukemia | NCT04007029 | Phase 1 study to examine the clinical response of bispecific CD19/CD20 CAR T-cells in R/R B-cell lymphoma | Recruiting |
| A Study to Assess the Anti-Tumor Activity and Safety of Odronextamab in Adult Patients With B-cell Non-Hodgkin Lymphoma Who Have Been Previously Treated With Other Cancer Therapies | NCT03888105 | Phase 1 study to examine effectiveness of odronextamab, CD3/CD20 bispecifc antibody in R/R B-cell lymphoma | Recruiting |
| Epcoritamab Plus Ibrutinib for the Treatment of Relapsed or Refractory Aggressive B-Cell Non-Hodgkin Lymphoma | NCT06536049 | Phase 1b/2 trial to examine the safety of combining epcoritamab, CD3/CD20 bispecific antibody with ibrutinib in R/R DLBCL, FL, HGBL, PMBL, and transformed lymphoma | Not yet recruiting |
| Lenalidomide and Blinatumomab for the Treatment of Relapsed Non-Hodgkin Lymphoma | NCT02568553 | Phase 1 trial to examine the combination of blinatumomab and lenalidomide in R/R NHL | Active, not recruiting |

Search for: Relapsed/Refractory Diffuse Large B-Cell Lymphoma, bispecific antibody | List Results | ClinicalTrials.gov. Accessed: October 31, 2024

# Final Thoughts …




- CAR T-cell therapy offers curative benefit for those patients that attain and maintain durable responses
  - Single treatment
  - Potentially curative
- Bi-specific Agents
  - Reasonable alternative after failure of CAR T-cell therapy
  - Established benefit and decent response rates after upfront CAR T-cell treatment
- Novel options
  - Combination chemotherapy regimens targeting multiple signaling pathways
  - Combination regimens with:
    - Bispecifics and chemotherapy
    - Bispecifics and CAR T-cell therapies
    - Bispecifics and immunomodulatory drugs
    - Bispecifics and immune checkpoint inhibitors
  - Incorporating checkpoint inhibitors into CAR constructs

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