Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: September 30, 2023

Citation: Tucker D and Thiebaud CM, 2023. An Overview of the Treatment of Non-Hodgkin Lymphoma with The Novel Cellular Therapies: CAR-T and Bispecific Monoclonal Antibodies, Medical Research Archives, [online] 11(9). https://doi.org/10.18103/mra.v11i9.4494

DOI
https://doi.org/10.18103/mra.v11i9.4494

ISSN: 2375-1924

LETTER TO THE EDITOR

An Overview of the Treatment of Non-Hodgkin Lymphoma with The Novel Cellular Therapies: CAR-T and Bispecific Monoclonal Antibodies

David Tucker*, Cristina M. Thiebaud

*Corresponding author: david.tucker1@nhs.net

ABSTRACT

The management of non-Hodgkin lymphoma (NHL), including refractory and relapsed high grade and low-grade NHL has been significantly improved in recent years with the development of cellular therapies which harness the powerful anti-cancer effects of the immune system. These include the ground-breaking and now established technology of chimeric antigen receptor cell therapy as well as the promising new range of bispecific monoclonal antibody therapies. This article will give a summary of the currently available cellular and bi-specific antibody therapies for the treatment of NHL in licenced use and clinical trials, including an overview of their proven efficacy and characteristic side-effect profiles which distinguish them from conventional immunochemotherapy. The relative strengths and weaknesses of these comparable therapies will also be discussed together with consideration of where they may fit into the treatment sequence of NHL in the future. The article will also address the challenges of delivering these innovative technologies in different healthcare settings and how they may alter the future of therapy for patients with this form of cancer.

Introduction:

Non-Hodgkin lymphoma (NHL) is the 6th most common cancer in adults in the UK and accounts for approximately 4% of all cancer diagnoses per year [1,2]. Two of the commonest subtypes of NHL are follicular lymphoma (FL) and diffuse large B cell lymphoma (DLBCL). Diffuse large B cell lymphoma is curable in approximately 65% of cases with standard immunochemotherapy but in those who relapse or are refractory to treatment the rates of durable remission with further treatment are low [3,4]. Follicular lymphoma, the commonest low-grade form of NHL, tends to respond well to immunochemotherapy with almost 90% survival for 5 years, however it is incurable, and patients achieve diminishing returns from treatment with each subsequent relapse. [5, 6]. Therefore, there is an unmet need in the treatment of R/R of FL and DLBCL. Targeted cellular therapies, including chimeric antigen receptor (CAR)-T cell therapy and bispecific monoclonal antibodies (BsAbs) are a novel therapeutic technology which recruit the patient's own cellular immunity to eradicate lymphoma cells. CAR-T cell therapy is more advanced than BsAb therapy in clinical trials and has already resulted in a paradigm shift in the management of relapsed DLBCL. The mechanism of action and side-effect profiles of both technologies are similar, however important differences in their manufacture and delivery mean both have distinct advantages and challenges. This letter will explore the emerging evidence for these two new therapeutic options, discuss their strengths and weaknesses and consider their future in the treatment landscape of NHL.

Non-Hodgkin Lymphoma

There are currently more than 60 subtypes of NHL which are classified by their clinical, immunohistological, and genetic properties [7,8]. Broadly, they can be characterised as low grade (indolent) or high grade (aggressive) lymphomas [9]. The commonest histological type of low-grade lymphoma is follicular lymphoma (FL), while the commonest high-grade lymphoma is diffuse large B cell lymphoma (DLBCL). In addition, there are several molecular classification systems used for DLBCL, confirming not only its complexity in gene expression, but also in the cellular origins and molecular entities in this pathology[10].

Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (RCHOP) has been the standard of care for DLBCL for decades with a 60% - 70% cure rate[11]. Recently, Pola-R-CHP, a modified drug combination that switches vincristine for polatuzumab vedotin has been licensed for patients with an International Prognostic Index of >2 and has superseded RCHOP by having a significantly superior progression-free survival[12].

Around 30 % of patients with DLBCL will relapse or be refractory to first line therapy. In approximately 50% of these relapses, remission can be achieved with second line immunochemotherapy and autologous stem cell transplantation[13]. However, many of those patients do not remain in a durable long-term remission. The prognosis is worse if relapse occurs within a year of first-line treatment when more than 70% of patients do not respond to second line immunochemotherapy[14]. To address this unmet need, cellular therapies such as CAR-T and BsAbs, have been studied in clinical trials. Successful clinical trials have led to the licensing of several CAR-T cell products for use after two prior lines of therapy and if patient fitness would allow for autologous stem cell transplantation. More recently, clinical trials of CAR-T cell therapy have broken new ground by moving up the therapeutic sequence: at first, relapse following RCHOP chemotherapy if that relapse occurs within a year of first line treatment[15]. Several BsAb products also show durable efficacy in DLBCL, but data are generally less mature than for CAR-T therapy. However, several products have gained FDA approval for use in this field [16, 17].

First line treatment of advanced FL normally comprises a CD20-specific monoclonal antibody, such as rituximab or obinutuzumab, combined with chemotherapy such as bendamustine, CHOP or cyclophosphamide, vincristine and prednisolone (CVP)[18,19]. Although FL is an indolent lymphoma and responds well to treatment, relapse is common with diminishing returns and cumulative toxicity from repeated use of conventional immunochemotherapy. Novel, chemotherapy-free approaches, including the use of BsAbs and CART cell therapy are currently demonstrating promising results in clinical trials of this scenario[20].

What Are Cellular Therapies?

CAR-T cell therapy and BsAbs are bio-engineered, cellular or monoclonal antibody constructs. Although structurally different, both work in a comparable way: by recruiting and harnessing the immune system to selectively destroy cancer cells according to target surface antigens. Although CAR-T technology has the most mature clinical trial data and is established in standard clinical practice, both demonstrate efficacy in the management of lymphoma and have relative strengths and weaknesses. It is possible that BsAbs will offer an alternative to CAR-T cell therapy in standard clinical practice in the future [21].

CAR-T cell therapy requires apheresis and subsequent, ex-vivo modification of a patient's T-lymphocytes which are genetically modified to express a hybrid T-cell receptor (TCR) which targets tumour-associated surface antigens (usually CD19). These autologous cells are then reinfused into the patient where they expand in number, bind and destroy tumour cells[22]. Several generations of CAR-T cell constructs have been developed, each improving on the last in terms of safety, durability and efficacy and aiming to address challenges related to off-target and off-tumour activity[23].

Bispecific antibodies, are monoclonal antibody constructs with dual specificity for a patient's unmodified T-lymphocytes (usually via the CD3 antigen) and B-lymphocytes (CD19). Although most remain at the pre-licencing phase of clinical trials, overall response rates have been encouraging[24]. Currently, there are around six BsAbs approved by the FDA and/or EMA for cancer, and two licensed for DLBCL[25].

What are the Adverse Effects of CAR-T and BsAb therapy?

Because of a similar mechanism of action, both CAR-T and BsAbs have comparable side-effect profiles although the frequency and severity of these effects vary between products. As well as common haematological toxicities such as anaemia, neutropenia and thrombocytopenia and the obvious risk of infection, this class of therapy have a distinct side effect profile which stems from the recruitment of the hosts immune system to destroy B-cells in a targeted manner. The most common manifestations of this are cytokine-release syndrome (CRS); immune effector cell-associated neurotoxicity syndrome (ICANS); tumour lysis syndrome (TLS) and pan-hypogammaglobulinaemia: a global reduction in humoral immunity which can be chronic and require immunoglobulin replacement therapy for infection prophylaxis.

Cytokine release syndrome is a systemic inflammatory response that can be triggered by a variety of factors and is commonly seen in varying degrees of severity in patients receiving CAR-T cell therapy or BsAbs. It is characterised by a range of symptoms from mild, flu-like symptoms to severe life-threatening manifestations of an over-active inflammatory response and tends to occur within hours or days of administration [26, 27]. Corticosteroids both as pre-dose prophylaxis and therapeutic doses and supportive care, are the mainstay of preventing and managing CRS. Disease-modifying anti-cytokine drugs such as tocilizumab, an anti-IL6 monoclonal antibody, are effective in patients with moderate to severe CRS. Early recognition of the signs and symptoms of CRS, (such as fever, bronchospasm, rash, hypotension) and early involvement of intensive care-support where necessary, are key in successful reversal.

Immune effector cell associated neurotoxicity (ICANS) is a poorly understood phenomenon of cellular and BsAb therapy and can vary in severity from dysphasia, tremor and mild delirium to seizures, reduced levels of consciousness and coma. Although there is some overlap with CRS, it is generally considered distinct in both pathobiology and presentation and tends to occur later than CRS. Close monitoring and surveillance are important as early recognition. Dose interruption and administration of corticosteroids can prevent more severe episodes [28].

A long-term reduction in humoral immunity due to depletion of the B-lymphocyte compartment, long-term infection risk including atypical infections and the risk of viral reactivation syndromes, particularly with cytomegalovirus, are well recognised with cellular therapy and BsAb use. Routine infection prophylaxis, particularly against Pneumocystis pneumonia (PJP); frequent monitoring for Cytomegalovirus (CMV) reactivation with regular viral RNA polymerase chain reaction assays are generally recommended and prompt treatment of a rising viral load is important to prevent disease.

The Efficacy of CAR-T in high grade lymphoma

There are currently 3 CAR-T therapies licensed for the treatment of relapsed / refractory (R/R) DLBCL: Tisagenleucel (Tisa-cel), Axicabtagene ciloleucel (Axi-cel) and Lisocabtagene maraleucel (Liso-cel)[29]. None of these agents have been compared directly in clinical trials and therefore any comparisons must be made with caution.

The ZUMA-1 trial, assessed Axicabtagene (an autologous anti-CD19 antigen receptor [CAR T cell therapy] in the treatment of refractory large B-cell lymphoma). It demonstrated durable responses in a heavily pre-treated patient group with a median overall survival of 25.8 months and a 5-year OS rate of 42.6%. Grade 3 neutropenia (78%), anaemia (43%) and thrombocytopenia (38%) were common and grade 3 or higher CRS and neurological events occurred in 13% and 28% of patients respectively [30, 31, 32]. Real world data appear to confirm these findings: a recent analysis performed by the Centre for International Blood and Marrow Transplantation Research (CIBMTR) confirmed an overall response rate (ORR) of 73%

and a 56% complete response (CR) rate with a comparable safety profile[33].

Tisagenlecleucel (Tisa-cel) and liso-cel are similar CAR-T constructs from different manufacturers and have demonstrated comparable efficacy in R/R DLBCL with a comparable adverse event profile[34, 35].

The TRANSFORM study brought CAR-T cell therapy forward in the therapeutic sequence to compare against autologous transplantation (ASCT) in patients with DLBCL at first relapse (provided this was within 1 year of initial induction chemotherapy). This was a pivotal study which challenged the paradigm of DLBCL management. It demonstrated clear superiority in favour of CAR-T cell therapy in this patient group and is changing standard practice in patients who relapse early and would be considered fit enough for ASCT[36]. As a result of these pioneering studies, CAR-T cell therapy has transformed the landscape for patients with R/R DLBCL in selected patients.

Not all patients with R/R DLBCL can receive CAR-T therapy for several reasons. Firstly, CAR-T cell therapy is generally regarded as suitable for patients who would normally be deemed fit enough to undergo intensive re-induction therapy with immunochemotherapy (although some referral centres will accept less fit individuals) - most patients with relapsed DLBCL do not meet this criterion. Referral to a specialist centre can take time and require significant travel for patients who live distant from a referral centre – this can be a challenge with an aggressive disease. T-cell apheresis is not always successful due to bone marrow exhaustion from prior therapy or disease infiltration. CAR-T cell manufacture can sometimes fail and currently requires approximately four weeks from apheresis to product readiness for re-infusion. During this time, it can be a challenge to maintain patient fitness and control of what is an aggressive relapsed disease until point of reinfusion.

Furthermore, the adverse events post infusion caused by immune-effector cell destruction of B cells (as outlined above) can be severe and require a level of baseline fitness which is often lacking in elderly patients wither relapsed disease. Despite these challenges, CAR-T cell is undoubtedly an effective therapeutic option for individuals with R/R DLBCL who are deemed fit enough and access is likely to improve as healthcare infrastructure learns to incorporate this therapy.

Bispecific Monoclonal antibodies (BsAbs) in high grade B cell lymphoma

Bi-specific monoclonal antibodies (BsAbs) are antibody constructs which engage endogenous T cells (typically via the CD3 antigen) and B-cell lymphoma cells (typically via the B cell antigen, CD19) in cell-dependent cytotoxicity. At the time of writing, there are approximately 6 distinct BsAbs in advanced development and two with FDA approval for use in relapsed DLBCL [16, 17, 37]. This technology builds on the use of "naked" monoclonal antibodies, such as rituximab: a unidirectional anti-CD20 monoclonal antibody, usually used in combination with chemotherapy which has demonstrated improved survival in several B-cell lymphomas and has paved the way for new anti-CD20 therapies [38]. Like rituximab, BsAbs have been used both as single agents and in combination with conventional chemotherapy.

Bi-specific Monoclonal Antibodies have a mechanism of action and characteristic adverse effects similar to CAR-T cell therapy in that they recruit the hosts immune system to destroy cancer cells[39]. They differ in several important ways which give them both strengths and weaknesses when compared with CAR-T therapy. Their manufacture, although complex, does not depend on apheresis and manipulation of patient T cells which has advantages in reducing manufacture failure rates, heterogeneity of production and the overall time taken to provide the treatment which can be a particular challenge in patients with aggressive disease. They can be distributed and stored more widely than a live cellular product which currently requires more specialised facilities thus there is a potential advantage of wider delivery and accessibility for patients living further away from specialist facilities. However, the currently available BsAbs require repeated intravenous or subcutaneous administration, whereas CAR-T cell therapy usually requires only a single infusion. This is a potential disadvantage; However, it does allow for dose manipulation and interruption which can help counteract some of the adverse effects. This may also reduce the severity of adverse effects such as CRS.

The data on safety and efficacy of BsAb therapy are less mature than those for CAR-T therapy. There are no data comparing any of these molecules directly with each other or with CAR-T cell therapy therefore any comparisons have to be made with caution. However, these molecules appear to be active against both relapsed DLBCL and low-grade forms of NHL such as FL.

Glofitamab has the most clinical data and has shown efficacy in patients with relapsed / refractory aggressive lymphoma including DLBCL and mantle cell lymphoma (MCL) with overall response rates of 48% and complete response rates of 39%. Common adverse events include neutropenia and low-grade CRS. Responses appear to be durable [16, 40]. Epcoritamab has also demonstrated comparable efficacy against DLBCL in clinical trials and has also obtained a licence for use in relapsed disease [17].

Mosunetuzumab and Odronextamab are other bispecific molecules which have demonstrated activity in the treatment of high-grade lymphoma as well as promising outcomes in the management of relapsed follicular lymphoma. These molecules are currently the subject of several trials in combination with immunochemotherapy and novel agents, such as lenalidomide in the management of FL [41, 42].

The Future for Cellular Therapies

Lymphoma treatment is an ever-evolving area, and although there are some uncertainties regarding the use of CAR-T and BsAbs, they have undoubtedly changed the treatment landscape. There are several important questions pertinent to their future use. Where they will be used in the sequence of treatment? Will BsAbs ultimately demonstrated comparable long-term safety and efficacy comparable with CAR-T and if so, should they be used as an alternative to or in sequence with CAR-T therapy? Should these drugs be part of front-line therapy in some individuals and how should those cases be selected? Should they be combined with other agents or be used as monotherapy? How can access be improved and how best to prevent and manage the unique characteristic side effect profile. Their prohibitive cost require consideration at a political level: some health care systems will undoubtedly struggle to provide or sustain this technology and the issue of inequity of access to advanced healthcare remains unresolved [43, 44].

It seems likely that there will be a place for both modalities in the therapeutic landscape because of the relative strengths and weaknesses of both. It is possible that a deeper understanding of the biology of the disease may allow us to better predict who may benefit most from cellular or bispecific antibody therapy and at what point in their cancer treatment.

Conclusion

Cellular therapies are exciting new developments which bring hope to patients with relapsed high- and low-grade lymphomas. Where they are best placed in the sequence of treatment is to be established. There is a need for more disease specific trials, better patient stratification and relationship to treatment, as well as clearer guidelines of when, how and where these novelty therapies should be implemented. Novel treatments bring with them as well, different toxicity profiles. Managing their side effects, reducing the costs, making them more freely available are all challenges for the future. Despite these challenges, cellular and BsAb therapy are undoubtedly revolutionising the management of non-Hodgkin lymphoma and represent an exciting technological breakthrough in cancer therapy.

Conflicts of Interest: Dr Tucker has received advisory board funding from Bei Gene, AbbVie, Roche and Immunovant Corps. Dr Thiebaud has none to declare.

Funding statement: None received.

References

1. Cancer Research UK » Non-Hodgkin lymphoma statistics. Accessed August 16, 2023. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/non-hodgkin-lymphoma
2. Howlader N, Noone AM, Krapcho M, et al. Cancer Statistics Review, 1975-2017 - SEER Statistics. National Cancer Institute. Published November 2019. Accessed August 15, 2023. https://seer.cancer.gov/archive/csr/1975_2017/
3. Epperla N, Vaughn JL, Othus M, Hallack A, Costa LJ. Recent survival trends in diffuse large B-cell lymphoma—Have we made any progress beyond rituximab? *Cancer Med*. 2020;9(15):5519-5525. doi:10.1002/CAM4.3237
4. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808. doi:10.1182/BLOOD-2017-03-769620
5. Tan D, Horning SJ, Hoppe RT, et al. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. *Blood*. 2013;122(6):981-987. doi:10.1182/BLOOD-2013-03-491514
6. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. *Journal of Clinical Oncology*. 2015;33(23):2516-2522. doi:10.1200/JCO.2014.59.7534
7. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390. doi:10.1182/BLOOD-2016-01-643569
8. WHO » WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Accessed August 22, 2023. https://www.iarc.who.int/news-events/who-classification-of-tumours-of-haematopoietic-and-lymphoid-tissues-2/
9. Bowzyk Al-Naeeb A, Ajithkumar T, Behan S, Hodson DJ. Non-Hodgkin lymphoma. *BMJ (Online)*. 2018;362. doi:10.1136/bmj.k3204
10. Vodicka P, Klener P, Trneny M. Diffuse Large B-Cell Lymphoma (DLBCL): Early Patient Management and Emerging Treatment Options. *Onco Targets Ther*. 2022;15:1481. doi:10.2147/OTT.S326632
11. Stegemann M, Denker S, Schmitt CA. DLBCL 1L—What to Expect beyond R-CHOP? *Cancers (Basel)*. 2022;14(6). doi:10.3390/CANCERS14061453
12. Tilly H, Morschhauser F, Sehn LH, et al. The POLARIX Study: Polatuzumab Vedotin with Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (pola-R-CHP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) Therapy in Patients with Previously Untreated Diffuse Large B-Cell Lymphoma. *Blood*. 2021;138(Supplement 2):LBA-1. doi:10.1182/BLOOD-2021-154729
13. González-Barca E, Boumendil A, Blaise D, et al. Outcome in patients with diffuse large B-cell lymphoma who relapse after autologous stem cell transplantation and receive active therapy. A retrospective analysis of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplantation 2019 55:2*. 2019;55(2):393-399. doi:10.1038/s41409-019-0650-x
14. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808. doi:10.1182/BLOOD-2017-03-769620
15. Westin J, Sehn LH. CAR T cells as a second-line therapy for large B-cell lymphoma: a paradigm shift? Blood. 2022;139(18):2737-2746. *Blood*. 2023;141(6):683-683. doi:10.1182/BLOOD.2022018793
16. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022;387(24):2220-2231. doi:10.1056/NEJMOA2206913
17. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. The Lancet. 2021;398(10306):1157-1169. doi:10.1016/S0140-6736(21)00889-8
18. Wang Y, Zhou S, Qi X, et al. Efficacy of front-line immunochemotherapy for follicular lymphoma: a network meta-analysis of randomized controlled trials. *Blood Cancer J*. 2022;12(1):1. doi:10.1038/S41408-021-00598-X
19. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. *New England Journal of Medicine*. 2017;377(14):1331-1344.

doi:10.1056/NEJMOA1614598/SUPPL_FILE/NEJMOA1614598_DISCLOSURES.PDF

20. Gordon MJ, Smith MR, Nastoupil LJ. Follicular lymphoma: The long and winding road leading to your cure? *Blood Rev*. 2023;57:100992. doi:10.1016/J.BLRE.2022.100992
21. Patel A, Oluwole O, Savani B, Dholaria B. Taking a BiTE out of the CAR T space race. *Br J Haematol*. 2021;195(5):689-697. doi:10.1111/BJH.17622
22. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J*. 2021;11(4):69. doi:10.1038/S41408-021-00459-7
23. Dagar G, Gupta A, Masoodi T, et al. Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments. *J Transl Med*. 2023;21(1):449. doi:10.1186/S12967-023-04292-3
24. Salvaris R, Ong J, Gregory GP. Bispecific Antibodies: A Review of Development, Clinical Efficacy and Toxicity in B-Cell Lymphomas. *J Pers Med*. 2021;11(5). doi:10.3390/JPM11050355
25. Lejeune M, Köse MC, Duray E, Einsele H, Beguin Y, Caers J. Bispecific, T-Cell-Recruiting Antibodies in B-Cell Malignancies. *Front Immunol*. 2020;11:520058. doi:10.3389/FIMMU.2020.00762/BIBTEX
26. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of Blood and Marrow Transplantation. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758
27. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018;6(1):56. doi:10.1186/S40425-018-0343-9
28. Jain, M. D., Smith, M., & Shah, N. N. (2023). How I treat refractory CRS and ICANS after CAR T-cell therapy. Blood, 141(20), 2430–2442. https://doi.org/10.1182/BLOOD.2022017414
29. Perales MA, Anderson LD, Jain T, et al. Role of CD19 Chimeric Antigen Receptor T Cells in Second-Line Large B Cell Lymphoma: Lessons from Phase 3 Trials. An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy. *Transplant Cell Ther*. 2022;28(9):546-559. doi:10.1016/J.JTCT.2022.06.019
30. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood*. 2023;141(19):2307-2315. doi:10.1182/BLOOD.2022018893/2035688/BLOOD.2022018893.PDF
31. Balke-Want H. Putting the pedal to the metal: axi-cel for LBCL. *Blood*. 2023;141(19):2285-2286. doi:10.1182/BLOOD.2023020188
32. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. Lancet Oncol. 2019;20(1):31-42. doi:10.1016/S1470-2045(18)30864-7
33. Jacobson CA, Locke FL, Ma L, et al. Real-World Evidence of Axicabtagene Ciloleucel for the Treatment of Large B Cell Lymphoma in the United States. *Transplant Cell Ther*. 2022;28(9):581.e1-581.e8. doi:10.1016/J.JTCT.2022.05.026
34. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *New England Journal of Medicine*. 2019;380(1):45-56. doi:10.1056/NEJMOA1804980/SUPPL_FILE/NEJMOA1804980_DISCLOSURES.PDF
35. 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. *The Lancet*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0
36. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *The Lancet*. 2022;399(10343):2294-2308. doi:10.1016/S0140-6736(22)00662-6
37. Falchi L, Vardhana SA, Salles GA. Bispecific antibodies for the treatment of B-cell lymphoma: promises, unknowns, and opportunities. *Blood*. 2023;141(5):467-480. doi:10.1182/BLOOD.2021011994/1928283/BLOOD.2021011994.PDF
38. Salles G, Barrett M, Foà R, et al. Rituximab in B-Cell Hematologic Malignancies: A Review of 20 Years of Clinical Experience. *Advances in Therapy 2017 34:10*. 2017;34(10):2232-2273. doi:10.1007/S12325-017-0612-X
39. Bock AM, Nowakowski GS, Wang Y. Bispecific Antibodies for Non-Hodgkin Lymphoma Treatment. Curr Treat Options Oncol. 2022;23(2):155-170. doi:10.1007/S11864-021-00925-1/METRICS

40. Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a Novel, Bivalent CD20-targeting t-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-Cell Lymphoma: A phase i trial. *Journal of Clinical Oncology*. 2021;39(18):1959-1970. doi:10.1200/JCO.20.03175
41. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;23(8):1055-1065. doi:10.1016/S1470-2045(22)00335-7
42. Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. Lancet Haematol. 2022;9(5):e327-e339. doi:10.1016/S2352-3026(22)00072-2
43. Cusatis R, Tan I, Piehowski C, et al. Worsening Financial Toxicity Among Patients Receiving Chimeric Antigen Receptor t-Cell (CAR-T) Therapy: A Mixed Methods Longitudinal Study. Blood. 2021;138(Supplement 1):567-567. doi:10.1182/BLOOD-2021-146032
44. Chacim S, Monjardino T, Cunha JL, et al. Costs, effectiveness, and safety associated with Chimeric Antigen Receptor (CAR) T-cell therapy: Results from a comprehensive cancer center. PLoS One. 2022;17(12):e0278950. doi:10.1371/JOURNAL.PONE.0278950