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A Novel Drug for Refractory Diffuse Large B-Cell Lymphoma (DLBCL)-A Review

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Review Article

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ABSTRACT

Epkoritamab, a subcutaneously injected CD3xCD20 T cell receptor, is the first and only bispecific antibody that activates T cells, directing them to attack $CD20^+$ B cells. It has been shown to increase immune response in DLBCL, FL and patients. MCL regardless of previous CD20 monoclonal antibody therapy. Its mechanism of action differs from other immunotherapy, such as CAR T cell therapy, which involves genetic modification of the patient's own T cells for cancer cells. FDA grants accelerated approval for epcoritab-bysp (Epkinly) as a third-line treatment for relapsed or refractory Diffuse Large B-Cell Lymphoma (DLBCL) of undetermined origin, including DLBCL and grade B cells caused by indolent lymphoma after two or more lymphomas gave many treatments. Non-Hodgkin Lymphoma (NHL) is a type of Large B-Cell Lymphoma (DLBCL). It is a cancer of the lymphatic system that occurs when the body produces abnormal B lymphocytes, which are white blood cells that normally help the body fight disease. There are several subtypes of DLBCL, including Central Nervous System (CNS) primary DLBCL, DLBCL not otherwise specified (NOS), and primary mediastinal (thymic) large B-cell lymphoma. DLBCL is usually treated with different types of chemotherapy, steroids, and a monoclonal antibody called rituximab. The R-CHOP regimen, representing rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, is effective in approximately 60% of patients and can eliminate the disease. But DLBCL can come back after treatment, and researchers are working to better understand the basis of the disease to develop new treatments and improve treatment outcomes. In this review, we discuss the expansion of epkoritamab in the treatment of refractory DLBCL.

Keywords: Refractory Diffuse Large B Cell Lymphoma (DLBCL); Epcoritamab; CD3xCD20 T-cell; Non-Hodgkin Lymphoma (NHL); Central Nervous System (CNS)

INTRODUCTION

A type of Non-Hodgkin Lymphoma (NHL), called Diffuse Large B-Cell Lymphoma (DLBCL), occurs when the body produces abnormal B lymphocytes (white blood cells that normally help fight disease). Like the spleen, liver, bone marrow or other tissues and organs, the lymphatic system is also the source of cancer. Swelling of lymph nodes, fever, night sweats, fatigue and weight loss are some of the signs and symptoms. Aggressive B-cell lymphoma is called grade B lymphoma. The most common symptoms of DLBCL are swollen lymph nodes (tumors) in the groin, neck, or neck; it may not hurt [1].

Approximately one-third of patients with DLBCL have fever, night sweats, and unexplained weight gain. These are the so-called "B symptoms". Also, most of them are skinny and have no appetite. After first-line treatment, 60% to 70% of DLBCL patients achieve Complete Remission (CR); however, up to 50% develop resistance to treatment or relapse [2].

Infection or stability after first-line treatment is called drug resistant DLBCL. If a disease reoccurs or worsens after resolution, this is called "relapse". Hematology oncologists treating patients with DLBCL still face challenges in treating such patients. Salvage high-dose chemotherapy combined with autologous stem cell transplantation is a popular treatment for patients with relapsed or refractory DLBCL. However, there are many approved and developed treatments for DLBCL, including CAR T cell therapy, immunotherapy, and targeted drugs [3]. Stem cell transplant is sometimes an option. More randomized controlled trials are needed to better understand the management and treatment of patients with relapsed or refractory DLBCL. Treatment plans for patients with relapsed or relapsing DLBCL should be tailored to the patient's age, comorbidities, and disease characteristics [4].

A new antibody called epkoritamab has been shown to be effective in treating relapsed or refractory DLBCL. The FDA approved Epkinly (epcoritab-bysp) injection for the treatment of adults with advanced B-cell lymphoma and for the treatment of patients who have relapsed after two or more chemotherapy regimens or refractory Diffuse Large B-Cell Lymphoma (DLBCL) Otherwise stated fused [5]. This includes DLBCL caused by indolent lymphoma. Epkinkly is administered subcutaneously or subcutaneously over a 28-day period or until infection or toxicity is tolerated. A bispecific vaccine called epkoritamab is being developed for the treatment of a type of B-cell non-Hodgkin lymphoma. It is a medication used to treat advanced B-cell lymphoma and Diffuse Large B-Cell Lymphoma (DLBCL) in adults [6]. Sometimes called EPKINLYTM or DuoBody®-CD3xCD20. Epkoritamab is a bispecific antibody that targets CD3 and CD20 proteins on the surface of cancer cells. AbbVie is developing it together with Genmab. In the EPCORETM NHL-1 clinical trial, Epcoritab was evaluated in patients with relapsed/refractory Large B-Cell Lymphoma (LBCL) and encouraging results were obtained. The FDA recently approved epcoritab-bysp for the treatment of relapsed or refractory diffuse large B-cell lymphoma as well as advanced B-cell lymphoma. A phase IA/II study is investigating the maximum dose of epkoritamab that can be used as an adjunct to chemotherapy in patients with B-cell non-Hodgkin lymphoma. Epcoritamab is not licensed for use outside clinical studies; now displayed [7].

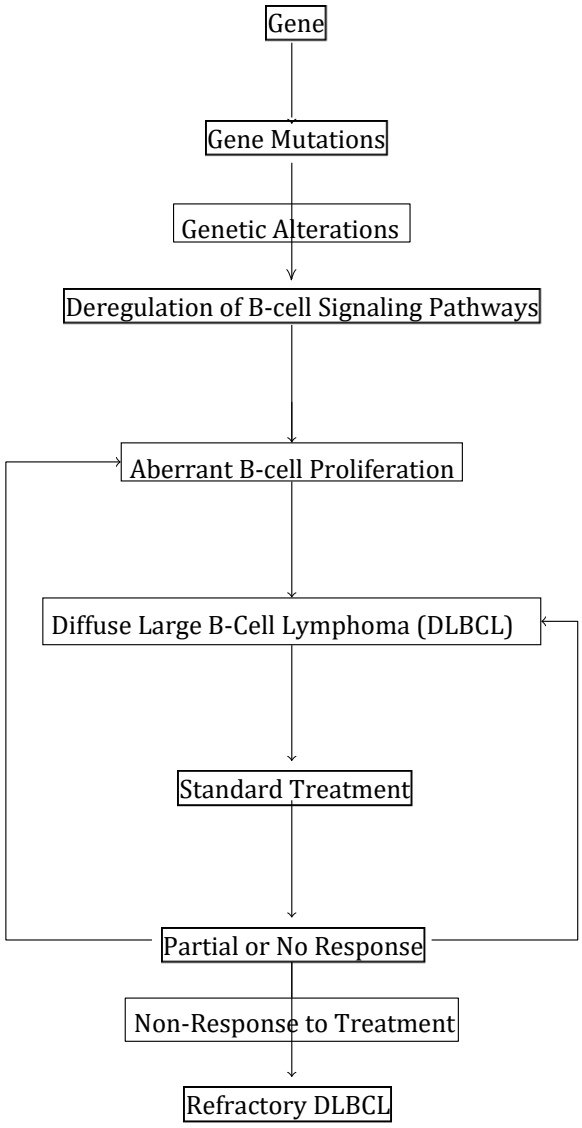
LITERATURE REVIEW

Pathogenesis of refractory diffuse large B-cell lymphoma

A type of lymphoma called Diffuse Large B-Cell Lymphoma (DLBCL) is characterized by the proliferation and maturation of large B cells. Recent studies have shown that various genetic alterations, such as chromosomal translocations, ASHM mutations, translocation mutations, and copy number alterations, affect DLBCL [8]. The pathophysiology of DLBCL is

associated with B cell-like gene expression in germinal regions, usually caused by genetic mutations. The type of lymphoma that may develop in a particular patient depends on the type of mutation and the level of development of lymphoid tissue at the time of the genetic abnormality. Different stages of B cell growth can lead to B cell lymphoma. DLBCL subtypes are the result of genetic changes during B cell maturation. Germinal center B cell DLBCL occurs when B cells are exposed to antigens that cause somatic hypermutation during the germinal center reaction phase (Figure 1) [9].

Figure 1: Treatment strategies for patients with diffuse large B-cell lymphoma.



Toll-Like Receptors (TLRs), BCR, CD40, B cell Activating Factor (BAFF), and other receptors are receptors activated by NFkB in DLBCL. The etiology of DLBCL is thought to be, in part, NFkB activation [10].

To achieve new changes in treatment, it is important to understand the main points and molecular pathways involved in the pathophysiology of DLBCL. Standard immune chemotherapy is effective in most cases of DLBCL; But the prospects of non-responders are generally poor [11]. Molecular pathways involved in DLBCL pathogenesis to develop new treatments. Why DLBCL has many subtypes, each with molecular characteristics, it is a heterogeneous disease [12]. To effectively treat refractory DLBCL, it will be important to target several pathways:

Nf-κb pathway: DLBCL, or drug-resistant diffuse large B-cell lymphoma, is a type of treatment-resistant lymphoma. The best chemotherapy for lymphoma must be treated differently [13]. The NF-κB pathway is a potential target for molecular therapy. An important factor in treatment resistance in relapsed and refractory DLBCL is the NF-κB pathway, a signaling system that plays a role in the development of DLBCL. The regulation of cell survival, proliferation and differentiation is mediated by this pathway. In Activated B Cell (ABC) DLBCL, downstream inhibitors of the NF-κB pathway, such as lenalidomide and the proteasome inhibitor bortezomib, have been shown to be effective [14]. However, various molecular abnormalities associated with signaling pathways other than NF-κB have been proposed as the cause of the immune response, from novel schemes for recycling and recycling of DLBCL.

A variety of methods need to be targeted to effectively treat refractory DLBCL. PI3K/mTOR, MAPK, NFAT and B Cell Receptor (BCR) signaling pathways are other targets of molecular therapy [15].

New treatments and drugs for DLBCL are being investigated, and precision medicine strategies that take into account DLBCL genetic subtypes may benefit treatment options.

B Cell Receptor signaling pathway (BCR): The B Cell Receptor (BCR) signaling pathway affects the development, survival and proliferation of malignant and healthy B cells. 40% of patients with B cell-like (ABC) DLBCL responded to ibrutinib, a drug that targets the BCR pathway, according to a phase 2 study of relapsed patients with advanced and refractory DLBCL. There are several different molecular subtypes of DLBCL, each with unique genetic and metabolic factors in BCR survival [16].

Genetic mutations affecting the critical BCR pathway are associated with DLBCL.

Many types of B-cell lymphoma have identified the BCR signaling pathway as a promising therapeutic target, and surrogate markers are being sought. B cell differentiation in non-Hodgkin lymphoma is believed to have a significant impact on tumor survival [17].

BCR activates a cascade of signals that ultimately lead to oncogenic NF-κB, PI3K/. Activate mTOR, MAPK and NFAT.

Generally speaking, the BCR signaling pathway is an important target for DLBCL treatment. The PI3K/mTOR signaling pathway is a therapeutic target for refractory Diffuse Large B-Cell Lymphoma (DLBCL) patients. The mammalian target of the protein kinase B (Akt)/rapamycin (mTOR) pathway, which regulates growth, development, and drug resistance, is impaired in some patients with DLBCL. Other carcinogenic processes, with the approval of the oral small molecule PI3K inhibitor idelalisib, inhibiting the PI3K pathway as a cancer treatment has become a reality. Idialisib inhibits PI3K/AKT/mTOR signaling and induces apoptosis in primary patient samples and lymphocytes [18].

Idelalisib has been shown to be effective in treating indolent diabetes when used alone or in combination with first-line treatment in phase I clinical trials. However, some patients with DLBCL develop resistance to idelalisib; in idelalisib-resistant DLBCL cell line clones, whole exome sequencing identified PI3KCA gain of function mutations. Several PI3K inhibitors, such as TGR-1202, AMG-319, INCB-40093, and CUDC-907, are in early clinical development [19].

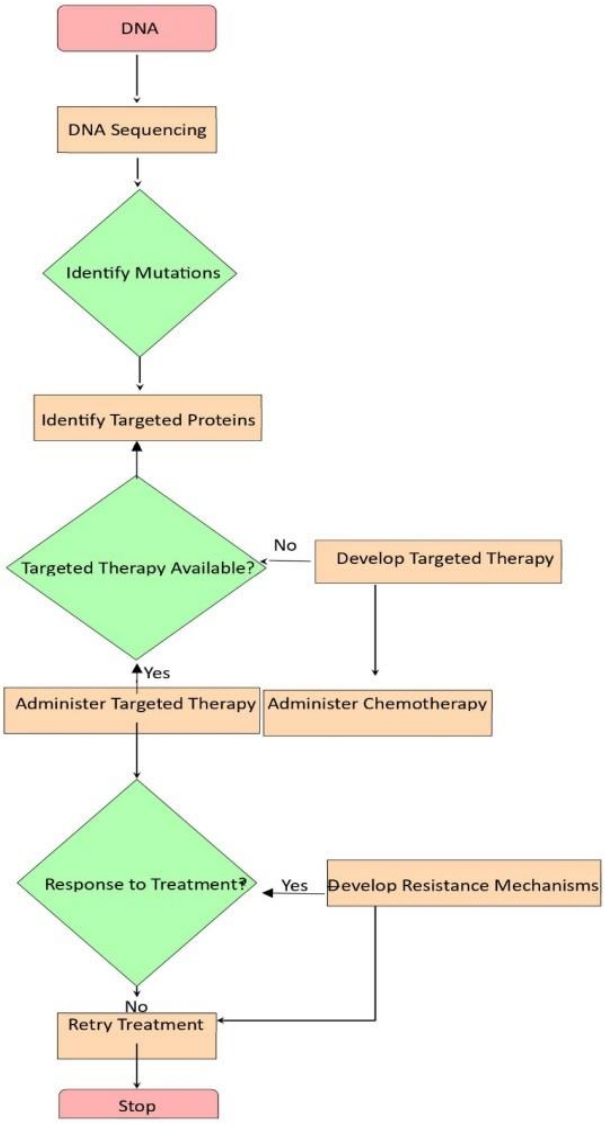
All types of lymphoma, including DLBCL, show activity against the mTOR inhibitors temsirolimus and everolimus, which may render DLBCL cells resistant to rituximab. While the Syk inhibitor fostamatinib has been shown to be effective in DLBCL, the PKC-β inhibitor enzastaurin has been used as combination therapy after DLBCL remission [20].

MAPK signaling pathway: The MAPK signaling pathway contributes greatly to the control of cell survival, differentiation and proliferation. RAS is a small GTPase that is frequently mutated in cancer, and it is this pathway that causes its downregulation. B Cell Receptor (BCR) activates signaling cascades leading to activation of NF-κB, PI3K/mTOR, MAPK, and NFAT pathways in Diffuse Large B-Cell Lymphoma (DLBCL). Deregulation of the RAS-MAPK pathway is associated with mature B-cell lymphoproliferative disorders. For DLBCL, inhibition of the MAPK pathway has been investigated as a potential therapeutic target. For example, the natural product TEOA has been shown to inhibit the growth and DNA damage of DLBCL

cells by activating the ROS-dependent p38 MAPK signaling pathway. Relapsed/refractory DLBCL is also associated with ERK activation and RAS-related protein transcription. In general, DLBCL is characterized by defects in various pathways that may have therapeutic potential, including MAPK signaling systems.

NFAT signaling pathway: The NFAT signaling pathway has been shown to contribute to the formation and progression of DLBCL. In DLBCL cells, B Cell Receptor (BCR)-mediated activation of NFATc1 activates the immunosuppressive IL-10/STAT3/PD-L1 signaling pathway. ABC DLBCL survival is mediated by enhanced NF-κB activation and acute BCR signaling. Activation of BCR results in signals that activate NF-κB, PI3K/mTOR, MAPK and NFAT pathways. Increases in the hexosamine biosynthetic pathway and O-GlcNAc metabolism are important for the growth of DLBCL cells. Deregulation of NF-κB and PI3K/Akt/mTOR pathway is common in DLBCL patients. The NFAT message is just one of many strategies that contribute to the growth and development of DLBCL. The use of small molecule inhibitors or other drugs that target this pathway may be helpful in treating refractory DLBCL (Figure 2).

Figure 2: Flow chat of DNA sequencing.



Immunotherapy: Epcoritamab

Immunotherapy has emerged as an effective treatment for patients with relapsed or refractory Diffuse Large B-Cell Lymphoma (DLBCL) that has not responded to previous treatment. The FDA approved Epcoritamab, the first and only T-cell associated bispecific antibody, in May 2023 for the treatment of adults with relapsed or refractory DLBCL. A new antibody called epkoritamab has been shown to be effective in treating relapsed or refractory DLBCL. It is a subcutaneous bispecific antibody that binds to CD20 and CD3 on T cells, causing B cells to be killed by T cells.

Approved by the FDA as a fast-acting and long-acting solution. FDA approval of epkoritamab was influenced by the Phase 1/2 EPCORE NHL-1 study (NCT03625037), which evaluated the drug in patients with refractory, increased CD20-positive mature B-cell non-Hodgkin lymphoma. performance or relapse in tumor patients. Patients treated with epkoritamab had a Complete Response Rate (CRR) of 30% and an Overall Response Rate (ORR) of 60%. In the open-label, phase 1/2 EPCORE NHL-1 study, Epcoritab was administered subcutaneously to patients over a 28-day period. The most common side effects associated with epkoritamab include fatigue, nausea, fever, and cytokine release syndrome.

RESULTS AND DISCUSSION

Mechanism

A CD3xCD20 bispecific antibody called epkoritamab binds to CD3 on T cells and CD20 on B cells. Many B-cell malignancies, including large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and chronic lymphocytic leukemia, have CD20 as a recognized therapeutic target.

Epkoritamab causes the destruction of lymphoma B cells by T lymphocytes. This bispecific vaccine uses Genmab's unique DuoBody technology to target cytotoxic T cells to tumors to weaken the immune system against cancer. In preclinical studies, Epcoritamab has been shown to have potent targeting T cell-mediated cytotoxicity against $CD20^+$ malignant B cells.

The difference from other anti-CD20 drugs is as follows:

- **Bispecific:** Capable of binding two types of antigens simultaneously. It specifically binds to CD3 on T cells and CD20 on B cells, bringing them together and activating T cells, thus killing B cells.
- **High response:** Epkoritamab demonstrated significant overall response in previously treated patients with Diffuse Large B-Cell Lymphoma (DLBCL).
- **Orphan drug designation:** FDA has designated it as an orphan drug; This means it can be used as an alternative treatment for patients with follicular lymphoma.
- **Well tolerated:** Epkoritamab has been shown to be both safe and effective in patients with relapsed and refractory large B-cell lymphoma.

Indications

Epkoritamab is recommended for the following diseases.

- Loj loj B cell lymphoma.
- Generalized locus B cell lymphoma, unspecified.
- Primary Mediastinal B-Cell Lymphoma (PMBCL).
- Qib B Cell Lymphoma (HGBCL).
- Follicular lymphoma, grade 3B.

FDA recommends increasing the epkoritamab dose in cycle 1 to 0.16 mg on day 1, 0.8 mg on day 8, and 48 mg on days 15 and 22.48 mg was given weekly for cycles 2 to 3, weekly for cycles 4 to 9, and every four weeks for the first day of progression (Table 1).

Dosage forms and strengths H3

Injectable solution, single-dose vial

- 4 mg/0.8 mL (dilute before use)
- 48 mg/0.8 mL

Table 1: B-Cell lymphoma disease dosage and recommendations.

Disease	Dose	Recommendation
B-Cell lymphoma	Cycle 1 • Day 1 (step-up dose 1): 0.16 mg SC x 1 dose • Day 8 (step-up dose 2): 0.8 mg SC x 1 dose • Day 15 (first full dose): 48 mg SC x 1 dose (hospitalize patient for 24 hr during first 48 mg dose) • Day 22: 48 mg SC x 1 dose	Indicated for relapsed or refractory Diffuse Large B-Cell Lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after ≥ 2 lines of systemic therapy Each cycle is 28 days See Administration for recommended pre-medications
	Cycles 2 and 3 • Days 1, 8, 15, and 22: 48 mg SC x 1 dose	
	Cycles 4-9 • Days 1 and 15: 48 mg SC x 1 dose	
	Cycle 10 and thereafter • Day 1: 48 mg SC x 1 dose • Continue until disease progression or unacceptable toxicity	

CONCLUSION

As a third-line treatment for patients with Large B-Cell Lymphoma (LBCL), epkoritamab is effective in treating patients with poor prognosis, such as double lymphoma or poor response to CAR T-cell therapy. It is well tolerated and does not lead to discontinuation of treatment due to side effects. Once patients complete their first cycle, the drug is well received and even becomes suitable for use in adults. He argues that there is another way for society to use Chimeric Antigen Receptor (CAR) T cell therapy. The majority of DLBCL responds to conventional chemotherapy; but non-responses are generally negative. This medicine works like a miracle for all unresponsive DLBCL.

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REFERENCE

1. Fundraising Regulator. Diffuse large B cell lymphoma. Cancer Research UK. 2022.
2. Lorenzo F, et al. A phase IA/II study of Epcoritamab in people with B-cell Non-Hodgkin Lymphoma. Memorial Sloan

Kettering Cancer Center. 2022.

3. Diffuse large B-cell lymphoma (DLBCL) symptoms and diagnosis. Blood Cancer UK. 2023.
4. Camille P, et al. Diffuse large B-cell lymphoma, causes, symptoms, diagnosis, treatment. WebMB. 2023.
5. Professional CC medical. Diffuse large B-cell lymphoma. Cleveland Clinic. 17 June, 2023.
6. Diffuse large B-cell lymphoma. Lymphoma action. 17 June, 2023.
7. Crump M, et al. Outcomes in refractory aggressive Diffuse Large B Cell Lymphoma (DLBCL): Results from the international scholar-1 study. Clinical Lymphoma Myeloma and Leukemia. 2016;16.
8. Diffuse large B-cell lymphoma: Relapsed/refractory. Lymphoma Research Foundation. 17 June, 2023.
9. Raut LS, et al. Management of relapsed-refractory diffuse large B cell lymphoma. South Asian J Cancer. 2014;3:66–70.
10. Center for Drug Evaluation and Research. FDA approves treatment for relapsed or refractory diffuse large B-cell. US Food and Drug. 17 June, 2023.
11. Diffuse large B-cell lymphoma: Symptoms, diagnosis, treatment. Healthline Media. 18 June, 2023.
12. Kesireddy M, et al. Relapsed or refractory diffuse large B-cell lymphoma: “Dazed and confused”. Oncol. 2023;36: 366-375.
13. Center for Drug Evaluation and Research. FDA grants accelerated approval to epcoritamab-bysp for relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma. FDA. June 18, 2023.
14. Gouveia GR, et al. Pathophysiology and molecular aspects of diffuse large B-cell lymphoma. Rev Bras Hematol Hemoter. 2012;34:447–451.
15. Schneider C, et al. Molecular pathogenesis of diffuse large B-cell lymphoma. Semin Diagn Pathol. 2011;28:167–177.
16. Michael G, et al. Diffuse large B cell lymphoma pathophysiology. Wikidoc. Jun 18, 2023.
17. Shipra GM, et al. Diffuse Large B-Cell Lymphoma (DLBCL). Medscape. June 18, 2023.
18. Lopez MA, et al. Diffuse large B-cell lymphoma pathophysiology. Rare Disease Advisor. June 18, 2022.
19. Roschewski M, et al. Molecular classification and treatment of diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma. Cancer J. 2020;26:195–205.
20. Roschewski M, et al. Diffuse large B-cell lymphoma treatment approaches in the molecular era. Nat Rev Clin Oncol. 2013;11:12–23.