Promising Novel Agents for Aggressive B-Cell Lymphoma

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KEYWORDS

• Diffuse large B-cell lymphoma • B-cell receptor • BCL2 inhibitor • EZH2 inhibitor

KEY POINTS

- DLBCL is the most common type of lymphoma in the western world.
- No single agent has been approved for the treatment of DLBCL in more than a decade.
- Agents targeting B-cell receptor signaling, Bcl2 protein, and PD1 immune checkpoint, have modest single-agent activity in relapsed DLBCL.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of adult lymphomas, accounting for approximately 25,000 new cases per year in the United States. Today, the most widely used regimen for the treatment of DLBCL is RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Historically, the CHOP regimen was introduced in the early 1970s. More than 40 years later, the only major therapeutic advancement has been incorporation of the monoclonal antibody rituximab with CHOP, creating the RCHOP regimen. Despite this progress, approximately 50% of patients have disease progression or relapse after RCHOP, and most die of their disease. Accordingly, new treatment modalities are necessary to improve the cure rate of patients with DLBCL.

At the molecular level, DLBCL is a heterogeneous disease. Hence, it is not surprising that many patients do not respond to standard RCHOP therapy. Gene expression profiling studies demonstrated that DLBCL is broadly classified into germinal center B-cell (GCB)-like and activated B-cell (ABC)-like subtypes. Using this "cell of origin" classification, it has been shown that treatment with standard RCHOP regime results in a better cure and overall survival in patients with the GCB subtype when compared with those with the ABC subtype. However, relapses are observed in both subsets after RCHOP therapy, suggesting the existence of additional oncogenic events that

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mediate resistance to RCHOP, irrespective of the cell of origin. More recent genome sequencing studies revealed a more complex molecular heterogeneity of DLBCL, with genetic alterations frequently observed in GCB and ABC subtypes. Other, less common genetic alterations can preferentially be detected in either GCB or ABC subsets. Novel treatment strategies that are based on lymphoma-associated oncogenic alterations are needed to improve the cure rate of patients with DLBCL.

One of the biggest challenges in drug development for patients with cancer, including DLBCL, is the high failure rate caused by excessive toxicity, low response rates, or both (Fig. 1). The success of future drug development in DLBCL depends on using biomarkers to identify patients who are likely to benefit from a specific therapy. The following is a focused review on the most promising agents for the treatment of DLBCL, with a discussion on how to select patients for these novel drugs based on genetic and molecular biomarkers. This article also provides a brief update on recent advances in immune therapy of DLBCL.

B-CELL RECEPTOR SIGNALING INHIBITORS

The B-cell receptor (BCR) complex is composed of membrane IgM that is linked with transmembrane heterodimer protein (CD79a/CD79b). Both CD79 proteins contain an immunoreceptor tyrosine-based activation motif in their intracellular tails. On BCR crosslinking by an antigen, the CD79a immunoreceptor tyrosine-based activation motif tyrosines (Tyr188 and Tyr199) are phosphorylated, creating a docking site for Src-homology 2 domain-containing kinases, such Lyn, Blk, and Fyn, with subsequent activation of downstream kinases, such as spleen tyrosine kinase (Syk) and bruton tyrosine kinase (Btk). Aberrant and sustained activation of BCR signaling pathway is implicated in the pathogenesis of a variety of B-cell malignancies, including DLBCL.

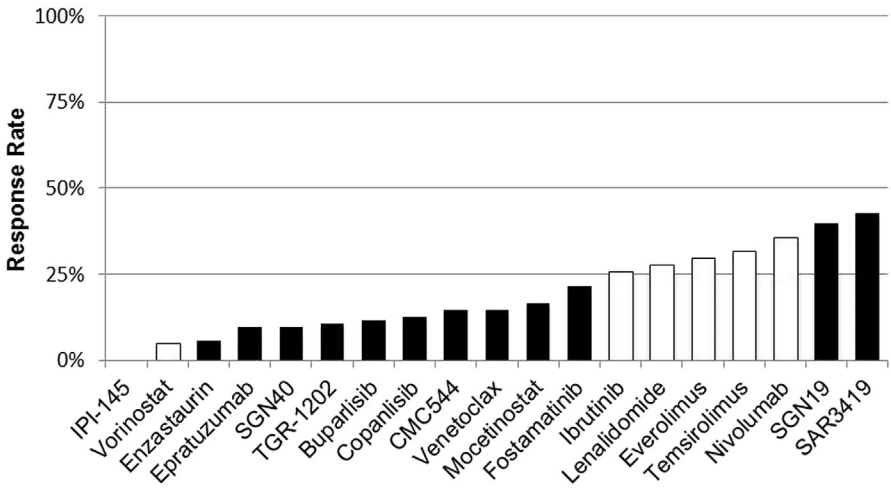

Fig. 1. Single-agent activity in patients with relapsed DLBCL. Results are generated from published data from phase I or phase II studies. Some of these trials are either ongoing and/or enrolled a small number of patients, and therefore these response rates may change with time. *Black bars* indicate investigational agents with no Food and Drug Administration–approved indication. *White bars* identify agents with Food and Drug Administration approval for different types of lymphoma, but none are approved for DLBCL.