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Oncogenic Signaling Pathways and Pathway-Based Therapeutic Biomarkers in Lymphoid Malignancies

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Abstract

Lymphoma is characterized by heterogeneous biology, pathologic features, and clinical outcome. This has been proven by accumulating pathologic and molecular evidence attributed to underlying aberrant alterations at genetic, epigenetic, transcriptional, protein, microenvironmental levels, and dysregulated oncogenic signaling pathways. In the era of precision medicine, targeting oncogenic pathways to design drugs and to optimize treatment regimens for the lymphoma patients is feasible and clinically significant. As such, further understanding of the biology and the mechanisms behind lymphoma development and identification of oncogenic pathway activation and pathway-based biomarkers to better design precise therapies are challenging but hopeful. Furthermore, pathway-based targeted therapies in combination with traditional chemotherapy, single specific targeted antibody therapy, and immunotherapy might raise the hope for the patients with lymphoma, especially for relapsed and refractory lymphoma patients.

Keywords

biomarker; lymphoma; oncogenesis; signaling pathway; therapeutic target

I. INTRODUCTION

Lymphomas are a group of hematologic malignancies which originate in lymphocytes and are characterized with heterogeneous outcomes and variable responses to standard of care regimens. Behind the heterogeneity, there are complex molecular mechanisms, mainly including aberrant genetic alterations and dysregulated oncogenic signaling pathways.^{1,2} Advances in biotechnologies and understanding of tumor biology are paving the way to

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identify these dysregulations and oncogenic biomarkers that can be targeted and can predict the response to the targeted therapy.³

In the era of precision medicine, the theme is to stratify patients based on the omics and accordingly to provide an optimal intervention on the risk-specific grouped patients.³ Such strategy has attracted more attentions in the field. As such, targeted therapy and immunotherapy have become the hottest therapeutic fields in recent years. Identifying underlying mechanisms and potential therapeutic biomarkers are biologically important and urgent for designing efficient cancer treatment regimens in the era of precision medicine.³

In this review, we evaluate several major dysregulated signaling pathways that contribute to oncogenesis of malignant lymphoma and valuable oncogenic biomarkers that present in these oncogenic pathways and have potential to be therapeutically targeted.

II. ONCOGENIC SIGNALING PATHWAYS IN LYMPHOMAS AND THEIR THERAPEUTIC POTENTIAL

Growing evidence supports that many dysregulated oncogenic signaling pathways contribute to the oncogenesis of a wide variety of malignancies, including lymphomas. The most frequently aberrantly regulated signaling pathways in the oncogenesis of malignant lymphomas include the B-cell receptor (BCR) pathway, the nuclear factor-kappaB (NF- κ B) pathway, the phosphoinositide-3-kinase/v-akt murine thymoma viral oncogene homolog1/mechanistic target of Rapamycin (PI3K/AKT/mTOR) pathway, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, the apoptosis pathway, and the programmed death-1/programmed death-ligands (PD-1/PD-Ls) pathway (Fig. 1). Some given signaling pathways are more preferentially enriched in specific types of lymphomas.

Targeting oncogenic signaling pathways that harbor oncogenic defects seem more feasible and are more applicable for the treatment of lymphoma patients than just based on the histological features. In fact, many pathway-based therapeutics have been demonstrated to have clinical activity across a broad variety types of lymphoma.

A. The BCR Signaling Pathway

The B-cell receptor is a transmembrane complex composed of a membrane-bound immunoglobulin that functions as an antigen-binding subunit and a linked heterodimer of CD79A/CD79B that acts to initiate and propagate signals. The signaling cascades and their corresponding targets control the precise function of normal B cells.^{4,5}

There are three types of BCR signaling pathways based on their modes of initiation: chronic active BCR signaling, tonic BCR signaling, and autonomous BCR signaling.

In the chronic active BCR signaling pathway, BCR aggregation upon antigen binding extracellularly has been proposed as an initial driver. At the same time of signal initiating, the immune receptor tyrosine-based activation motifs (ITAM) domain of CD79A and CD79B, the cytoplasmic tail of BCR, are phosphorylated by SRC family members. Subsequently, the phosphorylated ITAM recruits and activates the spleen-associated tyrosine

kinase (SYK). SYK thereby phosphorylates the Bruton tyrosine kinase (BTK) and the B-cell linker (BLNK), which act as key linker molecules to deliver multiple downstream signals, including the PI3K/AKT/mTOR signaling, the mitogen-activated protein kinase (MAPK) signaling, the NF- κ B signaling, and the NF-AT signaling. During the signal delivering process, AKT and BTK utilizing phosphatidylinositol (3,4,5)-trisphosphate (PIP3) as a docking site phosphorylate and activate the PI3K/AKT/mTOR and the NF- κ B pathway, respectively.^{2,6,7}

This classical antigen-dependent BCR signaling and its downstream signaling result in a variety of cellular functions, including proliferation, survival, apoptosis, as well as differentiation. It is frequently and aberrantly activated in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with low level IgM expression, in a subset of active B-cell-like (ABC) diffuse large B-cell lymphoma (DLBCL) bearing *CD79B* and *CARD11* mutations, in mucosa-associated lymphoid tissue lymphoma (MALT) with Hp infection, and in splenic marginal zone lymphoma with hepatitis C virus infection.^{2,8–10} With regard to the chronic stimulator, in addition to the driving aspects mentioned above, MALT1/API2 fusion and B-cell lymphoma 10 overexpression, *PI3K* mutation and phosphatase and tensin homolog (*PTEN*) gene loss of function are implicated in the oncogenesis of MALT and DLBCL, respectively.^{11,12}

The second BCR pathway, called tonic BCR signaling, is characterized with signals initiating through temporary and stochastic interplays between the BCR and the Lck/Yes-related novel protein tyrosine kinase (LYN) and SYK, independent of antigen stimulating and BCR aggregation.^{7,13} The tonic BCR pathway exists in normal B-cell function and is commonly observed in Burkitt lymphoma (BL) that bears some distinctly different genetic abnormality compared to other lymphoma types, such as in transcription factor 3 (TCF3) and inhibitor of DNA binding 3 (ID3) alterations.¹⁴

The third kind of BCR pathway called cell autonomous BCR signaling pathway has a specific feature in that BCR aggregates without external antigen but relies on an interaction between the two neighboring BCRs through CDR3 and FR2 crosslinking.¹⁵

Given that aberrantly activated BCR signaling has been increasingly implicated in oncogenesis of several types of B-cell hematologic malignancies, especially in CLL/SLL and ABC-DLBCL, the inhibitors targeting the BCR pathway render the patients with B-cell lymphomas an effective option for treatment.¹⁶ Several clinical trials targeting some oncogenic biomarkers in the BCR pathway and its downstream pathways have been showing promising efficacy to treat the malignant lymphomas with an aberrant signaling pathway activation (Tables 1 and 2).

B. The NF- κ B Pathway

The NF- κ B pathway, as one of the most common signaling pathways exists, and, functions transiently in normal lymphoid cells and several types of tissues. The constitutively activated NF- κ B pathway has also been implicated by accumulating evidence in oncogenesis of many types of human malignancies including lymphomas.^{2,17}

The NF- κ B pathway, categorized by canonical and noncanonical pathways, includes p50, p65(RelA), RelB, p52, and c-Rel proteins. These subunits present in patterns of homodimers or heterodimers that transduce their functional signals.

The canonical NF- κ B pathway is downstream of several signaling pathways, such as BCR, T-cell receptor (TCR), Toll-like receptor (TLR), and tumor necrosis factor receptor (TNFR) pathways. For example, in the downstream arm of the BCR pathway, the I κ B kinase (IKK) complex is phosphorylated by the CARD11/MALT1/BCL10 complex and, thereby, directly activates I κ B α . Activated I κ B α subsequently activates the RelA/p50 heterodimer, leading to translocation of RelA/p50 into the nucleus and the execution of final functions, such as cell survival/antiapoptosis, proliferation, inflammation, and innate immunity.

In the noncanonical NF- κ B pathway, the involved RelB subunit forms a heterodimer with its partner p52 or p50; the activators of the noncanonical signaling are preferentially BAFF-R and the IKK complex that contain two IKK α are activated by the NF- κ B-inducing kinase (NIK). The target genes of the noncanonical NF- κ B pathway function in lymphoid organogenesis, adaptive immunity, anti-inflammatory properties, and B-cell maturation.^{18–20}

The constitutively activated canonical and non-canonical NF- κ B signaling pathways can be observed more or less in almost all types of lymphoma. Particularly, ABC-DLBCL is the type affected by NF- κ B through various mechanisms.²¹ These oncogenic events may partly result from a dysregulated upstream chronic active BCR signaling in which *CARD11* and *CD79B* mutate or from the myeloid differentiation primary response 88 (*MYD88*)^{L265P} mutation.^{8,9,22} Additionally, other oncogenic events, such as dysregulated upstream of the JAK/STAT pathway, NF- κ B target genes alteration, chromosomal translocation, or EBV infection, may also contribute to the constitutive activation of the NF- κ B pathway in ABC-DLBCL, MALT, BL, Hodgkin lymphoma (HL), or other types of lymphoma.^{2,18}

The inhibition to the NF- κ B pathway can be carried out by directly inhibiting NF- κ B components or indirectly by inhibiting its upstream pathways. For example, the inhibition of p-I κ B α using Bortezomib, a proteasome inhibitor, is a rational option for treating patients with constitutive NF- κ B pathway activities and has shown good efficacy for DLBCL patients in combination with traditional chemotherapy.²³ Another p-I κ B α blockade, MLN 4924, was shown activity in mantle cell lymphoma (MCL) and DLBCL, regardless of the germinal center B-cell-like or the ABC subtype.^{24–26}

C. The PI3K/AKT/mTOR Signaling Pathway

The PI3K/AKT/mTOR signaling pathway is activated following the BCR pathway, the TNFR pathway, or other upstream pathways, and functions as a regulatory part in cell growth, survival, apoptosis, proliferation, metabolism, and motility processes.^{27,28} The PI3K family consists of four major isoforms on the basis of different structures and functions. Among the PI3 kinases, PI3K δ and PI3K γ are preferentially critical to B- and T-cell development and immune function.^{28–30} In the PI3K/AKT signaling, PI3K delivers an active signal to AKT through PIP3 which acts as a docking site for AKT; this process can be negatively regulated by PTEN.³¹ Then, AKT as a principal oncogenic effector of this pathway targets many molecules and executes its functions.³² These include the indirect

activation of the mTOR complex 1 (mTORC1) and the mTOR complex 2 (mTORC2), which increase mRNA translation, protein synthesis, and cellular proliferation or negatively regulate this pathway with a negative feedback.^{28,33}

The aberrant activation of the PI3K/AKT/mTOR pathway can confer oncogenicity in many types of cancer. This oncogenic activation is commonly related to *PIK3CD* mutation in DLBCL, loss of function *PTEN* in GCB-DLBCL, and *PIK3CA* copy number increasing in MCL.^{34–36} Moreover, p-AKT has been shown to be overexpressed and acts as an inferior outcome indicator in DLBCL, MCL, and peripheral T-cell lymphoma.^{37–39} Considering the critical status of the PI3K/AKT/mTOR pathway in lymphoma, PI3K, AKT, and mTOR are all potential targets to design drugs for the treatment of lymphoma patients (Tables 1 and 2).

D. The JAK/STAT Signaling Pathway

The JAK/STAT pathway is an essential signaling pathway as a key mediator of cytokine signaling, in which a network of molecules is involved and functions aberrantly. Cytokines, cytokine receptors, JAKs and STATs participate in the positive regulation of the JAK/STAT pathway, while tyrosine phosphatases, inhibitors of STATs, suppressor of cytokine signaling (SOCS) proteins, and cytokine-inducible SH2-containing (CIS) protein are the negative regulators.^{40–42} Upon binding of cytokines, basally inactive JAKs engaged to cytokine receptors are phosphorylated and, thereby, phosphorylate STATs. After dimerization, phosphorylated STATs translocate from the cytoplasm to the nucleus and then bind targeted genes, causing transcriptional activation and functioning in apoptosis, survival, proliferation, angiogenesis, and metastasis. This pathway, in turn, is negatively regulated through SOCS and CIS.

The underlying molecular mechanisms in the dysregulation of the JAK/STAT pathway in lymphoma still remain unclear. But major aberrations like *JAK2* aberration are accompanied by Jumonji domain-containing protein 2C (*JMJD2C*) abnormality, loss-of-function mutation of *SOCS1*, and protein tyrosine phosphatase non-receptor type 2 (*PTPN2*) deletion may all be contributors to the oncogenic JAK/STAT signaling in primary mediastinal B-cell lymphoma (PMBL), classical Hodgkin lymphoma (cHL), and ABC-DLBCL.^{40,41,43–45} Particularly, aberrations of STAT3, STAT5, and JAK2 have been shown to be the most common signature in these malignancies.^{40,46–48}

The increasing evidence described above has paved the way for targeting the JAK/STAT pathway to treat hematologic patients with a dysregulated JAK/STAT pathway. The inhibitors targeting JAKs, STATs, or ILs, and other related biomarkers have been developed or are under investigation. They are being expected to show efficacy in lymphoma via many rational ways such as inducing growth arrest and inhibiting angiogenesis (Fig. 2, Tables 1 and 2).^{47,49,50}

E. The Apoptosis Signaling Pathway

Apoptosis is a process of programmed cell death that occurs naturally and is critical for the normal organism development, biological evolution, internal environmental stability, and abnormal cells clearance. This process, being a complex network, is controlled by a series of

highly conserve molecules, like the BCL2 family, the caspase family, and the tumor suppressor protein p53.⁵¹

The apoptosis pathway can function via at least two distinct but interconnected pathways: the extrinsic and the intrinsic apoptosis pathways. One of the extrinsic apoptotic pathways is triggered by some death receptors outside a cell upon ligands binding, rapidly activating death caspases and subsequently causing apoptotic signaling cascades. Among the death receptors, Fas and TNFR-1 are the well-known and best-characterized death receptors, which bind their correspondent ligands. Fas and its cofactor, fas-associated via death domain (FADD), and caspase 8 form a death-inducing signaling complex that commits the cell to apoptosis through direct activation of downstream caspases such as caspase 3 and caspase 7, or through the mitochondrial-dependent pathway, which involves the release of cytochrome C, formation of apoptosome, activation of caspase cascades, and regulation by the BCL2 family.^{52,53} Similarly, after being activated, TNFR1 forms complexes with many death domain-containing proteins like TNFRSF1A associated via death domain (TRADD), TNF receptor associated factor 2 (TRAF2), thereby committing the cell to apoptosis through ways that Fas mediates, or recruiting IKK and finally activating NF- κ B function.^{54,55}

The intrinsic apoptosis pathway occurs mainly due to intracellular stresses, including oncogenic stress, DNA damage, as well as hypoxia. This intrinsic apoptosis pathway related with the mitochondria is mediated by p53 which interacts with other upstream or downstream DNA checkpoint proteins and BCL2 family members. Similar to the extrinsic pathway, the final effectors of the intrinsic pathway are caspase 3 and caspase 7, which cause proteolysis and apoptosis.^{52,56,57}

In the pathologic process, the normal apoptosis signaling pathway is interrupted by oncogenic defects and cells grow unchecked, leading to the oncogenesis of a wild variety of cancer, including hematologic malignancies. Interfering pathologic apoptosis pathway and restoring its normal function seem to have therapeutic potential. Among the therapeutic targets, BCL2, MYC, and p53 might be the suitable target candidate (Fig. 3, Tables 1 and 2).

F. The PD-1/PD-Ls Signaling Pathway

PD-1 and PD-Ls are harnessed by the immune system to balance its immune function. Upon binding to its ligands, PD-1 delivers co-inhibitory signals, negatively regulating the functions of T and B cells to maintain the immune balance.⁵⁸ However, in the cases of tumor, overexpression of PD-Ls in tumor cells and infiltrating cells, owing to genetic alteration, virus infection, or other intrinsic and extrinsic factors, can activate PD-1 signaling and lead to exhaustion of effector T cells after the interaction of PD-1 and PD-Ls.^{59,60} Such an immune escaping signaling has been demonstrated to be a major mechanism contributing to oncogenesis, tumor aggression and metastasis.⁵⁹

Apart from the PD-1/PD-Ls signaling, many other immune checkpoint pathways and molecules function between tumor cells and their surrounding microenvironment. Many costimulatory signals and coinhibitory signals participate in this pathway, which modulates a strict immune function, such as cytotoxic T-lymphocyte associated protein 4 (CTLA-40/CD86/CD80, B- and T-lymphocyte-associated/Herpes virus entry mediator A (BTLA/

HVEM), lymphocyte activating 3/major histocompatibility complex II (LAG-3/MHCII), and T-cell immunoglobulin mucin receptor 3 (TIM-3)/Galectin9 (Fig. 4).⁶¹

Agents blocking these immune checkpoint path ways bring a promise to treat a broad spectrum of malignancies. For relapsed/refractory cHL, DLBCL, and follicular lymphoma (FL), immune checkpoint blockades showed encouraging efficacy. Among these blockades, antibodies targeting PD-1 or PD-L1 are the current focus. More and more of the checkpoint inhibitors have been approved and translated into clinical immunotherapy management (Tables 1 and 2).^{59,61}

G. The Complex Interplay Among Different Oncogenic Pathways in Lymphomas

Detailed genomic and biologic studies have revealed the complexity of different oncogenic pathway networks in lymphoma. Many oncogenic pathways are independent but interconnected in a specific type of lymphoma. One type of lymphoma attributes to several dysregulated pathways that interact with each other; one activator can activate several pathways; one pathway may act as upstream or downstream of other pathways; and some molecules function as key points involved in several pathways. The complex crosstalk among the different oncogenic pathways may contribute to oncogenesis and heterogeneity of lymphoma, raising questions about how to design efficient therapeutic drugs targeting these complex oncogenic pathways and how to prevent targeted drugs from resistance and toxicity.

III. THERAPEUTIC BIOMARKERS RELATED TO ONCOGENIC PATHWAYS IN LYMPHOMAS

It is well known that targeted therapies are established toward specific biomarkers that might be key components of oncogenic pathways or other related molecules in cases of mutation, deletion, translocation, and overexpression. These biomarkers can be tested by means of DNA, RNA, or protein using reliable and reproducible technique platforms. In addition to being targeted for rational drugs design, some of these biomarkers might be able to predict treatment outcome and to be used for the selection of patients who may benefit from the pathway-based therapy management.

A. BCL2

BCL2 is encoded by the *BCL2* gene located on chromosome 18q21.3. As a member of the BCL2 family and an apoptosis regulator, BCL2 functions to suppress apoptotic death by interacting with caspases and other BCL2 family members. The BCL2 family includes antiapoptotic and proapoptotic members, which programmatically control cell death. Among them, BCL2 is the key molecule at the crossing point in the apoptosis pathway that is involved in cell survival, apoptosis, and proliferation.^{62,63}

t(14;18)/*IgH/BCL2*, involving *BCL2* juxtaposed with *IgH*, is a molecular hallmark of FL and can be found in GCB-DLBCL.^{64,65} But interestingly, *BCL2* is essentially untranslocated but is frequently amplified in the ABC-DLBCL subtype.^{66,67} Both translocation and overexpression were identified to be associated with some types of lymphoma with aggressive clinical features and adverse outcome.

All the BCL2 family members have a BCL2 homology domain (BH). Particularly, the BH3 domain is the region that can be frequently mimicked to develop inhibitors through binding BCL2 or BCL-XL.⁶⁸

BCL2 appears to be an ideal druggable target to develop its inhibitor. Obatoclax is such a BCL2 inhibitor that can restore apoptosis. Obatoclax can be used as a single agent to treat relapsed/refractory HL and to treat previously untreated FL while in combination with Rituximab.^{69,70} Venetoclax (ABT199), another BCL2 inhibitor, offers promise to patients with relapsed/refractory lymphoid malignancies.⁷¹

B. p53

p53, a nuclear transcription factor, regulates the expression of a broad variety of target genes involved in physiological cellular functions. As a tumor suppressor protein, p53 functions as an important mediator in the apoptosis pathways under oncogenic stress, DNA damage, and hypoxia through transcriptional activation of pro-apoptotic BCL2 family members and repression of antiapoptotic BCL2 proteins, inducing cell apoptosis and growth arrest.^{72,73}

p53 inactivation and the dysregulation of p53 signaling pathway contribute to oncogenesis of cancers at various frequencies. Abnormality of components in the p53 pathway, like MDM2 or p14ARF, are frequent oncogenic events in cancers, including in lymphomas.^{72,74}

Therapeutically, the p53 pathway-targeting appears rational to treat p53-related malignancies. Mechanistically, such therapeutic approaches may include to restore the tumor suppressor function of p53, to block MDM2-p53 interaction, and to reactivate p53-mediated apoptosis pathways, using p53-delivering adenovirus, MDM2 inhibitors, and vaccine.^{72,75–77} APG-115, an MDM2 inhibitor, has shown antitumor activities in multiple human cancer xenografts and is being expected to show efficacy and safety in advanced solid tumors and lymphomas (Clinical Trials Registration: NCT02935907).

C. Myc

The proto-oncogene *Myc* encodes the Myc protein, which is a typical pleiotropic transcription factor and is involved in almost every process of cell biology and oncology by regulating thousands of target genes.^{78,79} In many aggressive cancers, including aggressive lymphomas, Myc functions as a driver along with other cofactors, involving in oncogenesis, malignant transformation, and aggressive clinical features.

The chromosomal translocation of *Myc* often presents in some aggressive lymphomas, typically in BL and a subset of DLBCL. *Myc* on chromosome 8q24 is juxtaposed with one of the heavy- or light-chain immunoglobulin gene loci on the derivative chromosome 14 or other, which is defined as t(8;14) (q24;q32), t(2;8)(p12;q24), or t(8;22)(q24;q11).^{78,80} The small subset of DLBCL in which the *Myc* translocation occurs along with *BCL2* or *BCL6* is generally described as double-hit lymphoma or triple-hit lymphoma, which confers adverse outcomes. Similar to the double-hit lymphoma, the double-expression lymphoma, which is characterized with Myc and BCL2 co-overexpression, also exhibits inferior prognosis.

Unlike other oncogenic biomarkers, Myc itself was not considered druggable because of its unique structure and function. Alternatively, targeting options include Myc activation by reducing MycC/Myc associated factor X (MAX) heterodimerization, and DNA binding, targeting Myc-associated chromatin modification, targeting cell-cycle kinases, and interfering with its downstream target genes.⁸¹ For example, the bromodomain containing protein 4 (BRD4) now acts as an important and promising target whose inhibitors, JQ1 and RVX2135, are small molecules to downregulate Myc function and expression. JQ1 also shows efficacy in multiple myeloma and other Myc-driven malignancies.^{82–84} Another indirect Myc inhibitor is Alisertib, a selective Aurora A kinase inhibitor, which has been shown to induce response in relapsed/refractory aggressive B- and T-cell lymphomas. Aurora A is essential in Myc-driven lymphoma.⁸⁵ AZD5153, an available BET/BRD4 inhibitor, has a rational potential for the treatment of hematologic malignancies owing to its antitumor activity by transcriptionally affecting Myc, E2F, and mTOR.⁸⁶

D. BTK

BTK, a member of the Tec family, is a cytoplasmic tyrosine kinase and is mainly expressed in B cells and myeloid cells but not in plasma cells and T cells. Its normal function is limited in B cells. In addition to its critical function in B lymphocyte development and differentiation, BTK is an indispensable component for BCR signaling, responsible for being activated by SYK and subsequently phosphorylating and activating phospholipase C $\gamma 2$ (PLC $\gamma 2$) and protein kinase C β (PKC β). Phosphorylated PLC $\gamma 2$ and PKC β finally trigger the downstream NF- κ B pathway, which can induce multiple genes with antiapoptotic reaction and cell survival.^{16,87,88} In addition, BTK plays key roles in the TLR pathway and cytokine receptor signaling pathway, that are involved in immune function, transcription regulation, and apoptosis modulation.⁸⁹

BTK as a therapeutic biomarker can be targeted by its inhibitors to interrupt BCR signaling and NF- κ B signaling. Treatment with ibrutinib (PCI-32765) has been shown to induce considerable efficacy to patients with untreated and relapsed/refractory CLL, ABC-DLBCL, FL, MCL, marginal zone lymphoma, and lymphoplasmacytic lymphoma.^{90–93} However, ibrutinib may have certain limitations. First, some lymphomas do not just depend on the BCR and NF- κ B pathways but may depend on other BTK-independent pathways or genetic mutations; therefore, these lymphomas may show constitutive resistance to ibrutinib. Second, BTK has shown to take part in other pathways apart from the BCR pathway. Ibrutinib in combination with bendamustine and rituximab is also being tested for treatment of relapsed/refractory aggressive non-Hodgkin lymphomas, including PMBL, double-hit lymphoma, transformed indolent lymphoma, high-grade B-cell lymphoma, and CLL/SLL.^{94,95} Other BTK inhibitors, such as acalabrutinib (ACP196), ONO/GS-4059, BGB3111, and M7583, are being evaluated in various clinical trials.^{96,97}

E. SYK

SYK, another cytoplasmic nonreceptor-type tyrosine kinase, is extensively expressed in B cells, T cells, and myeloid cells and regulates a diverse range of cell functions, including adaptive immunity, cell adhesion, and vascular development.⁹⁸ SYK is indispensable for the maturation of B cells, especially at the differentiation stage from pro-B to pre-B, and

functions downstream of the BCR signaling pathway.^{16,99} SYK directly binds the phosphorylated ITAMs of CD79A/B or is phosphorylated by activated LYN, and thereby phosphorylates and activates BLNK or PKC β , ultimately generating downstream signaling effects.^{16,100} SYK is also involved in T cells differentiation and T-cell receptor signaling.¹⁶

One of inhibitors of SYK, Fostamatinib (R406, R788), has been evaluated in several types of lymphoma and showed effects on some lymphomas. Among them, the highest response rate is 55% in CLL patients. The response rate in DLBCL, MCL, and FL was 22%, 11%, and 10%, respectively.^{16,101}

F. PI3Ks

The PI3K family comprises three classes of kinases with different structures and functions. Class I is most commonly involved in cancer and contains four isoforms: p110 α , p110 β , p110 δ , and p110 γ .²⁸ p110 δ , encoded by *PIK3CD*, is generally expressed in leukocytes and the thymus, and it acts to activate signaling cascades to influence cell growth, proliferation, survival, and morphology through the PIP3 function. p110 γ , encoded by *PIK3CG*, is involved in immune function. PI3Ks, as important kinases, are involved in the PI3K signaling, particularly p110 δ and p110 γ , and play essential roles in B-cell, T-cell, and NK-cell development, proliferation, migration, as well as cytokine production.^{28,102,103}

The representative inhibitor of the p110 δ iso-form is idelalisib, which has been shown clinical activity in relapsed CLL, MCL, FL, and DLBCL. The efficacy of idelalisib in lymphoma may result from the direct effect of inhibiting p110 δ or the indirect effect of controlling the microenvironmental signals such as cytokines and chemokines secretion.^{103–105} Other pan-class I PI3K inhibitors include buparlisib (BKM120), SAR245408, and BAY 80-6946;²⁸ duvelisib (IPI-145) is an inhibitor against p110 δ /p110 γ isoform, which shows efficacy in both T- and B-cell lymphomas.^{106,107}

G. AKT

AKT belongs to the serine/threonine kinase and acts as a downstream mediator of the PI3K pathway, targeting numerous target genes and regulating biological processes related to cell survival, growth, proliferation, and angiogenesis.

AKT as a therapeutic target can be inhibited by inhibitory agents. Perifosine, a first-generation inhibitor against AKT, has not been put into clinical practice owing to its moderate toxicity.^{108,109} MK-2206 is a second-generation AKT inhibitor used for trials in patients with relapsed/refractory lymphoma.¹¹⁰ Notably, the phosphorylated-Akt protein expression by immunohistochemistry from pre- to post treatments can be used as a prognostic or predictive biomarker to assess the outcome or treatment response.^{38,39}

H. mTOR

mTOR, a serine/threonine-protein kinase, regulates cellular metabolism, survival, and growth, by regulating the phosphorylation of thousands of target proteins. Both of mTORC1 and mTORC2 use mTOR as a functional and structural unit and the phosphorylated activation comes from upstream AKT. Activated mTORC1 positively regulates mRNA

translation and protein synthesis and negatively regulates autophagy. mTORC2 regulates cellular processes including cell survival and cytoskeleton organization.

Concerning mTOR inhibitors, most of the present agents inhibit mTORC1. Temsirolimus alone or combined with rituximab showed 38% and 59% of objective response rates in relapsed MCL, respectively.¹¹¹ Temsirolimus has also been evaluated in FL, CLL/SLL, and other aggressive lymphomas.¹¹² Another mTORC1 inhibitor, Everolimus, has also shown preclinical or clinical efficacy in a variety of relapsed aggressive lymphomas, including DLBCL, HL, and even T-cell lymphoma.^{113–115} A new inhibitor targeting both mTORC1 and mTORC2 is also being developed and tested in lymphoma and is being looked to for its greater efficacy with minimized toxicity.

I. PTEN

PTEN, known as a tumor suppressor gene, normally functions through suppression of the PI3K/AKT/mTOR pathway.¹¹⁶ Loss-of-function of the PTEN protein, resulted from genetic mutation and deletion, abnormal epigenetic regulation, as well as dysregulated protein–protein interactions, may lead to elevated AKT and mTOR activities which promote tumor growth.^{117,118} The PTEN-deficient lymphomas mainly include GCB-DLBCL (~11%) and MCL, suggesting the exclusive role of the functional deficiency of PTEN in oncogenesis of these lymphomas.^{38,66}

As for the therapeutic implication of PTEN, it mainly relies on the inhibition of some components of the PI3K/AKT/mTOR pathway. This is due to the fact that inactivation of PTEN is significantly associated with activation of the PI3K/AKT/mTOR pathway.^{117–119} Such inhibitory agents include the pan-PI3K inhibitor like buparlisib, the p110 δ -specific PI3K inhibitor like idelalisib, and the mTOR inhibitor like everolimus,^{105,113,120} which have the potential to intervene in both advanced solid tumors with PTEN deficiency and PTEN-deficient lymphomas.

J. STATs

The STATs family includes seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. These DNA-binding proteins play a critical role in survival, proliferation, and immune modulation.¹²¹ Significantly elevated expression of STAT3, IL6, and IL10 can be seen in ABC-DLBCL, which commonly shows constitutive NF- κ B pathway activation.^{48,122} STAT3 and STAT5 activation in cutaneous T-cell lymphoma are also unique features.¹²³ In anaplastic large T-cell lymphoma, STAT3 is upregulated significantly, partly owing to the nucleophosmin-1/anaplastic lymphoma receptor tyrosine kinase (NPM-1/ALK) fusion.¹²⁴ In contrast, STAT6 mutation occurs in 36% of PMBL and 11% of FL.¹²⁵ Given the therapeutic potential of STATs, pyrimethamine, a STAT3 inhibitor for the treatment of relapsed CLL/SLL, is in phase I/II study sponsored by the Dana-Farber Cancer Institute (Clinical Trials Registration: NCT01066663); SD1008 is a STAT3/JAK2 inhibitor, which could induce apoptosis.¹²⁶

K. JAKs

JAKs are JAK family members composed of four cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and tyrosine kinase 2. JAK1 and JAK2 mainly function in hematopoiesis and host defense, while JAK3 and TYK2 basically participate in the immune response. The JAKs aberrations in lymphomas have been demonstrated and implicated in oncogenesis. Aberrant JAK2 and JMJD2C amplification have been shown as a significant signature in cHL and PMBL, frequently accompanying with loss of function SOCS1 and PTPN2, which are negative regulators of the JAK/STAT pathway.^{40,41,45,50} The JAK2/SEC31A fusion involving t(4;9)(q21;p24) has been commonly seen in cHL;¹²⁷ the JAK2/PCM1 fusion deriving from t(8;9)(p22;p24) in patients with T-cell lymphoma has also been reported.¹²⁸ The JAK2/FLT3 fusion has been reported, and its inhibitor pacritinib (SB1518) was designed to treat relapsed/refractory cHL, FL, and DLBCL and demonstrates clinical safety and efficacy.^{50,129} JAK3 mutations can be found in NK T-cell lymphoma and adult T-cell leukemia/lymphoma, and may be involved in cytokine-independent JAK/STAT activation.^{130,131} Tofacitinib, a JAK3 inhibitor, has therapeutic potential to treat EBV-associated NK- and T-cell lymphomas by decreasing STAT5 phosphorylation, suppressing proliferation, and reducing EBV latency.¹³²

L. Interleukin 6 (IL-6)

IL-6, as a pleiotropic cytokine, functions in inflammation and B-cell maturation and acts as an initiator of the JAK/STAT pathway, the PI3K/AKT pathway, and the RAS/MAPK pathway.¹³³ IL-6 also acts to promote tumor, including IL-6-driven B-cell lymphoma transformation.¹³⁴

Targeting IL-6 or IL-6 receptor using monoclonal antibodies or inhibiting IL-6-related pathway to treat IL-6-driven malignancies is becoming feasible and promising.¹³⁵ Siltuximab (CNTO-328), an IL-6 ligand-inhibiting monoclonal antibody, has been evaluated in B-cell non-Hodgkin lymphoma, multiple myeloma, and Castelman disease.^{96,134,136}

M. MYD88

MYD88 is an activator of both NF- κ B and JAK/STAT signaling pathways by stimulating TLR/IL-1 receptor signaling. The TLR/IL-1/MYD88 signaling pathway has also been implicated in oncogenesis of a broad range of malignancies and has therapeutically targeted potential.²² *MYD88*^{L256} mutation is identified as a hallmark of LPL/WM and can also be found in a portion of ABC-DLBCL (~30%), primary central nervous system lymphoma (PCNSL), and marginal zone B-cell lymphoma (MZL).²² One study has made an attempt to develop drugs to inhibit MYD88 homodimerization on the basis of its structural and functional domains to block MYD88-dependent pathways like the TLR and IL-1 pathways.¹³⁷ IMO-8400, an oligonucleotide, used to inhibit ligands activation of TLRs7, 8, and 9, has completed its phase I/II clinical trial for the treatment of relapsed/refractory ABC-DLBCL with *MYD88*^{L265P} mutation (Clinical Trials Registration: NCT02252146). Another therapeutic strategy to treat ABC-DLBCL or other malignancies bearing aberrant MYD88 is to selectively inhibit interleukin-1 receptor-associated kinase 4 (IRAK4), which is responsible for all the biological function of MYD88.¹³⁸

N. PD-1 and PD-Ls

PD-1, encoded by programmed cell death 1 (*PDCDI*) at locus 2q37.3, is mainly expressed on activated T-cells. PD-1 functions as an inhibitory cell surface receptor to negatively regulate effector T-cell functions via phosphatases Src homology region 2 domain-containing phosphatase (SHP)-1/2-mediated inhibition toward TCR/CD3/ZAP70 signaling. PD-1 can also affect cell differentiation and survival by affecting cell survival factor Bcl-xL and effector function-associated transcription factors.^{58,139}

PD-L1, also called B7-H1, is encoded by *CD274* and is normally expressed on antigen-presenting cells while PD-L2, is encoded by programmed cell death 1 ligand 2 (*PDCD1LG2*), is mainly expressed on activated dendritic cells and some macrophages. PD-L1 overexpression in lymphoma cells and stromal cells may result from many different mechanisms. Apart from common amplification or translocation at 9p24.1, activation by other oncogenic pathways like the JAK/STAT or AP1 pathways, viral infection, and chemokines could mediate the constitutive expression of PD-L1. In the microenvironment, as overexpressed PD-L1 engaging to PD-1, effector T-cells are gradually exhausted, leading to immune function impairment and malignant cells escape from immune clearance.^{58,59,139}

In many lymphomas, PD-1 and PD-Ls are aberrantly expressed with variable degrees and different patterns attributed to distinct histone types and different molecular mechanisms. *CD274* amplification on chromosome 9q24.1 and PD-L1 overexpression are typical features in nearly 40% of cHL, 70% of PMBL, a small part of ABC-DLBCL and ALK+ anaplastic large T-cell lymphoma.^{60,140,141} In contrast, in FL and CLL/SLL, PD-1-positive infiltrating T cells are observed to be increased in lymph node follicles or CLL tumor cells;^{142,143} in virus-associated lymphomas, not only PD-L1 overexpression is especially significant but PD-1 expression on nonmalignant infiltrating T-cells is also increased.^{140,144,145} Meaningfully, the aberrant expression of PD-1 and PD-L1 has been associated with patient outcome and treatment response. Therefore, the immunohistochemical expression of PD-1 and PD-L1 can be used as predictive biomarkers.^{142,146,147} The study about PD-L2 and CTLA-4 expressions or other checkpoint molecules in lymphomas remains rare or absent.

Targeting by PD-1/PD-L1 pathway has been demonstrated to be a very encouraging strategy in a variety of tumors, including solid tumors and hematologic malignancies.^{148,149} Monoclonal antibodies targeting PD-1, pidilizumab, nivolumab and pembrolizumab, all have been approved to be used and have shown encouraging efficacy in hematologic malignancies, including cHL, PMBL, FL, CLL/SLL, particularly in relapsed/refractory patients or in combination with autologous hematopoietic stem cell transplantation.^{59,148,150–152} Some other PD1/PD-L1 monoclonal antibodies against PD-L1 are also under clinical evaluation in patients with solid tumors and hematologic malignancies. Durvalumab, atezolizumab, and avelumab are the representative anti-PD-L1 agents which have been approved by the FDA for the treatment of some solid tumors.^{153–155}

IV. PERSPECTIVES AND CHALLENGES

With the advance of biotechnology, especially NGS, and further understanding of the mechanisms of disease, identifying responsible oncogenic signaling pathways and

biomarkers became manageable. While more and more investigations are focusing on immunotherapy, the combination of targeting genetic defects and modulating immune functions through immunotherapy holds promise in treating tumors in the era of precision medicine.

However, numerous critical challenges stand in front of precision medicine for lymphoma treatment. First, although pathway-based oncogenic biomarkers are rationally of good values to be as targets rather than targets without oncogenesis involvement, the present targeted drugs did not show ideal and adequate effects in some lymphoma patients; this might be due to tumor heterogeneity and the complex interactivity among oncogenic pathways in lymphoma. Therefore, it is imperative to select 'driver' oncogenic biomarkers to develop drugs or to guide the selection of patients who may likely benefit from targeted drugs. Nonetheless, identifying such optimal "driver" oncogenic biomarkers will be a major challenge. It requires further understanding of the pathobiology and the mechanisms. Fortunately, numerous investigators are on their way to elucidate the biology and mechanisms at the genetic, epigenetic, transcriptional, protein, and microenvironmental levels.

Additionally, patient stratification based on oncogenic pathways will be another outstanding problem. Reliable and reproducible biomarkers to accurately convey activated oncogenic pathways in clinical patients will be needed. For example, PD-L1 expressed on the tumor cells can be used as a predictive biomarker to evaluate the response to the PD-L1 blockade. But in practice, the robustness of PD-L1 may depend on the specificity and sensitivity of the antibody, the platform or method to test, the status of intra-tumor heterogeneity, and other factors.

Like other tumors, many subtypes of lymphoma may be characterized by several and different oncogenic pathways. For this reason, it is challenging to determine whether the combination of multiple pathway inhibitors will be more effective than a single targeted agent, and how the best targeted combination can be chosen. Combination regimens should be established using predictive biomarkers from individual patients, and long-time validation should be carried in large cohort. Moreover, pathway-based targeted agents combined with traditional chemotherapy or immune checkpoint therapies might be optimal options for treating lymphoma patients.

As noted, the heterogeneity behind the biology, pathologic feature, molecular and clinical outcomes in lymphoma still stands in the way of precise medicine. Same as in practice, more attention should be given not only to further detailed insights of disease heterogeneity and underlying mechanisms but also to many issues related to heterogeneity, such as drug resistance, biomarker screening, biomarker testing, disease diagnosis, and patient selection. Particularly, effectively overcoming the resistance of pathway-based therapeutics is the major problem that researchers and clinicians must face.

Until now, precision medicine seems to be a paradox. Precision oncology pairing patients with malignancies with drugs for mutations or "pathway" mutations has been questioned. Some people debate whether the termed precision medicine or precision oncology will truly

bring the greatest medical breakthrough at the price of significant cost and too high expectation. For this matter, the objective understanding of the advantages and disadvantages of precision medicine will be rational.

V. CONCLUSION

Oncogenic signaling pathways and their harboring oncogenic alterations have been well recognized to play important roles in the development of lymphoma. In the era of precision medicine, identifying the activation of these oncogenic pathways and oncogenic biomarkers to pair patient treatment strategies with pathway-based targeted therapy is imperative and valuable. It is challenging, but it still holds promise. Lymphoma is complex and heterogeneous in diagnosis and treatment, which require more effort by investigators and physicians, and there is long way to go. Pathway-based targeted therapy in combination with traditional chemotherapy, single, specific, targeted antibody therapy, and immunotherapy raise hope for the patients with lymphomas, especially for relapsed and refractory lymphoma patients.

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ABBREVIATIONS

ABC	active B-cell
AKT	V-AKT murine thymoma viral oncogene homolog1
BCR	B-cell receptor
BL	Burkitt lymphoma
BTk	Bruton tyrosine kinase
cHL	classical Hodgkin lymphoma
CLL	chronic lymphocytic leukemia
DLBCL	diffuse large B-cell lymphoma
FL	follicular lymphoma
GCB	germinal center B-cell
HL	Hodgkin lymphoma
IKK	I κ B kinase

IL-6	interleukin 6
ITAM	immune receptor tyrosine-based activation motifs
JAK	Janus kinase
MALT	mucosa-associated lymphoid tissue lymphoma
MCL	mantle cell lymphoma
MDM2	double-minute 2 protein
mTOR	mechanistic target of rapamycin
mTORC	mTOR complex
MYC	v-Myc avian myelocytomatosis viral oncogene homolog
MYD88	myeloid differentiation primary response 88
NF-κB	nuclear factor-kappaB
PD-1	programmed death-1
PD-Ls	programmed death-ligands
PI3K	phosphoinositide-3-kinase
PIP3	phosphatidylinositol 3,4,5-trisphosphate
PKCβ	protein kinase C β
PMBL	primary mediastinal B-cell lymphoma
PTEN	phosphatase and tensin homolog
SLL	small lymphocytic lymphoma
STAT	signal transducer and activator of transcription
SOCS	suppressor of cytokine signaling
SYK	spleen-associated tyrosine kinase
TLR	Toll-like receptors
TNFR	tumor necrosis factor receptor

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FIG. 1.

Illustration of cross-communication network of BCR, PI3K, and NF-κB signaling pathways that harbor effective therapeutic targets in lymphoma. BCR signaling, PI3K/AKT/mTOR signaling, and NF-κB signaling are independent but interconnected and may form complex crosstalk network. One pathway may act as upstream or downstream of other pathways and some molecular targets function as key points and players involved in several pathways. These key molecules have been shown promise to be a good therapeutic target for effective treatment in lymphoid malignancies. (A) Tonic BCR signaling pathway and PI3K/AKT/mTOR signaling pathway; (B) chronic active BCR signaling; (C) canonical NF-κB signaling pathway; (D) noncanonical NF-κB signaling pathway. The arrows indicate direction of activating signaling steps; the light-colored bars indicate inhibitory signaling steps; the black bars show inhibition from therapeutic agents toward targets. BAFF-R, B-cell activating factor receptor; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CARD11, caspase recruitment domain family, member 11; IKK, IκB kinase; MALT1, mucosa-associated lymphoid tissue lymphoma translocation protein 1; NEMO, NF-κB essential modifier; NIK, NF-κB-inducing kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3 kinase; TCR, T-cell receptor; TLRs, Toll-like receptors; TNFR, tumor necrosis factor receptor.

FIG. 2.

Illustration of JAK/STAT signaling pathway that inspires effective therapeutic targets in lymphoma. JAK/STAT pathway is a key mediator of cytokine signaling in both physiological and pathological conditions. Upon binding cytokines, basally inactive JAKs engaged to cytokine receptors are phosphorylated and thereby phosphorylate STATs. After being dimerization, phosphorylated STATs translocate from cytoplasm to nucleus and then bind to specific targeted genes. In turn, this pathway is negatively regulated by SOCS and CIS. The inhibitors targeting JAKs, STATs, or ILs are being expected to show expected treatment efficacy in some lymphomas. JAK, Janus kinase; STAT, signal transducer and activator of transcription; SHP, Src homology region 2 domain-containing phosphatase; SOCS, suppressor of cytokine signaling; CIS, cytokine-inducible SH2-containing protein; PI3K, phosphoinositide-3-kinase; AKT, v-akt murine thymoma viral oncogene homolog1; mTOR, mechanistic target of Rapamycin; ERK, extracellular signal-regulated kinase; CCND1, cyclin D1; VEGF, vascular endothelial growth factor.

FIG. 3.

Overview of apoptosis signaling pathway that contains effective therapeutic targets in lymphoma. The naturally occurring apoptosis pathway functions through extrinsic and intrinsic signaling and is controlled by a series of highly conserve molecules. Interfering pathologic apoptosis pathway and restoring its normal function seem to have therapeutic potential in many types of cancer. Among these therapeutic targets, BCL2, MYC, and p53 might be the suitable target candidates. FasL, Fas ligand; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; FADD, fas associated via death domain; TRADD, TNFRSF1A associated via death domain; BID, BH3 interacting domain death agonist; tBID, truncated BID; BAX, BCL2 associated X; BCL2, B-cell lymphoma 2; BAK, BCL2 antagonist/killer; Myc, v-Myc avian myelocytomatosis viral oncogene homolog; ARF, alternate open reading frame; MDM2, mouse double-minute 2 protein; ATR, Ataxia telangiectasia and Rads-related protein; ATM, ataxia telangiectasia mutated; chk2, checkpoint kinase 2.

FIG. 4.

Overview of PD-1/PD-Ls signaling pathway that acts as effective therapeutic targets in lymphoma. Upon binding to its ligands PD-Ls, PD-1 delivers co-inhibitory signals, negatively regulating T-cell function to maintain immune balance. In the cases of tumor, overexpressed PD-Ls activate PD-1 signaling, leading to exhaustion of effector T cell after interaction of PD-1 and PD-Ls. Targeting PD-1 and/or PD-L1 are the current focus of immunotherapy and clinical management in several solid tumor and hematologic malignancies. APC, antigen presenting cell; PD-1, programmed death-1; PD-L, programmed death-ligand; MHCII, major histocompatibility complex, class II; TCR, T-cell receptor; SHP, Src homology region 2 domain-containing phosphatase; ZAP70, zeta chain of T cell

receptor associated protein kinase 70; PI3K, phosphoinositide-3-kinase; AKT, v-akt murine thymoma viral oncogene homolog1; ERK, extracellular signal-regulated kinase; FOXO-1, forkhead box 1; mTOR, mechanistic target of Rapamycin; NFAT, nuclear factor of activated T cells; NF- κ B, nuclear factor-kappa B.

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TABLE 1

Pathway-based therapeutically oncogenic biomarkers and their biological characteristics in lymphomas

Oncogenic Biomarker	Gene and Location	Related Signaling Pathways	Typically Upstream or Downstream Targets	Protein Description	Biological Functions	Oncogenic Modes	Mainly Involved Lymphoma Types
BCL2	BCL2, 18q21.33	Apoptosis pathway	p53, BAD, BAX, BAK, CDK1	Anti-apoptotic protein	Suppresses apoptotic death	Translocation, amplification, overexpression	FL, DLBCL
Myc	MYC, 8q24.21	Apoptosis pathway	CyclinD1, CyclinD2, CDK4, CDK6, BLIMP-1, MAX, p27KIP1, p21, p14ARF, SMAD3	Proto-oncogene protein, pleiotropic transcription factor	Involves in cell cycle progression, apoptosis and cellular transformation	Translocation, overexpression, mutation	BL, DLBCL
p53	TP53, 17p13.1	Intrinsic apoptosis pathway	p14ARF, MDM2, ATM, ATR, p21, chk1, PUMA, NOXA, BAX	Nuclear transcription factor	Regulates transcription; Regulates cell cycle; Induces growth arrest or apoptosis	Mutation, inactivation	MCL, CLL/SLL, BL, DLBCL, PMBL, HL
BTk	BTk, Xq22.1	BCR, NF-κB, TLR, cytokine receptor signaling pathway	LYN, SYK, PLCγ2, PKCβ, MYD88, TLR8, TLR9	Cytoplasmic tyrosine kinase	Modulates B-cell development, immune function, transcription, and apoptosis	Aberrant activation	CLL/SLL, ABC-DLBCL, FL, MCL, MZL
SYK	SYK, 9q22.2	BCR, NF-κB, TCR, IL-2 signaling, PI3K pathway	BTk, SHP-1, BLNK, IKZF1, ROS, PLCγ1, STAT3	Cytoplasmic non-receptor type tyrosine kinase	Regulates B-cell differentiation, T cells differentiation, adaptive immunity, cell adhesion, and vascular development	Aberrant activation	CLL/SLL, DLBCL, FL, MCL
PI3Kδ	PIK3CD, 1p36.22	PI3K/AKT/mTOR, BCR, apoptosis, NF-κB pathway, JAK/STAT pathway	PIP3, AKT1, N-Ras, H-Ras, K-Ras, PI3K	Serine/threonine protein kinase	Involves in cell growth, proliferation, survival, and morphology	Mutation	DLBCL, FL, MCL
PI3Kγ	PIK3CG, 7q22.3	PI3K/AKT/mTOR, BCR, TLR/ MYD88 pathway	PIP3, AKT1, N-Ras, H-Ras	Serine/threonine protein kinase	Involves in B-cell, T-cell, and NK cell development, proliferation, migration, and cytokine production	Aberrant activation	B-cell lymphoma and T-cell lymphoma
AKT1	AKT, 14q32.33	PI3K/AKT/mTOR, BCR, apoptosis, JAK/STAT pathway, NF-κB pathway	PI3Kδ, MDM2, BAD, FOXO, Raf1	Serine/threonine protein kinase	Regulates cell survival, growth, proliferation, and angiogenesis	Mutation, overexpression	DLBCL, MCL, PTCL
mTOR	MTOR, 1p36.22	PI3K/AKT/mTOR, BCR, apoptosis, JAK/STAT, NF-κB pathway	AKT1, MAPKAP1, RPS6KB1, RPS6KB2, STAT1, STAT3	Serine/threonine protein kinase	Regulates cellular metabolism, survival, growth; mTORC1 regulates mRNA translation, protein synthesis, and autophagy; mTORC2 regulates cell survival and cytoskeleton organization	Aberrant activation	CLL/SLL, DLBCL, FL, MCL, and other aggressive lymphoma
PTEN	PTEN, 10q23.31	PI3K/AKT/mTOR, BCR, p53 pathway	miRNA17-92, AKT1, STAT5, PI3K	Tumor suppressor	Negatively modulates cell cycle progression, cell survival, proliferation, and migration	Mutation, inactivation	GCB-DLBCL, MCL, PTEN-deficient lymphomas
STAT3	STAT3, 17q21.2	JAK/STAT, EGFR, PI3K/AKT pathway,	EGFR, STAT1, Myc, mTOR, CyclinD1, JAK1, JAK2, TYK2, Src	Signal transducer and activator of transcription	Involves in cell growth and apoptosis	Mutation	NK/T cell lymphoma, cutaneous T-cell lymphoma, ALK+ALCL

Oncogenic Biomarker	Gene and Location	Related Signaling Pathways	Typically Upstream or Downstream Targets	Protein Description	Biological Functions	Oncogenic Modes	Mainly Involved Lymphoma Types
STAT6	<i>STAT6</i> , 12q13.3	JAK/STAT pathway, IL-4 signaling pathway	JAK1, JAK2, MAPK8, SHP-1	Signal transducer and activator of transcription	Activates transcription, involves in IL-4 signaling, induces antiapoptotic activity	Mutation	PMBL, FL
JAK2	<i>JAK2</i> , 9p24.1	JAK/STAT pathway, IFN γ signaling pathway	STAT6, SOCS-1, SOCS-3, STAT1, STAT3, IL-6R, IFN γ R1, EZH2, SHP-1	Nonreceptor tyrosine kinase	Involves in cell growth, development, and differentiation; mediates adaptive and innate immunity	Amplification, overexpression, JAK2/SEC31A fusion, JAK2/PCMI fusion, JAK2/FLT3 fusion	cHL, FL, DLBCL, PMBL, T-cell lymphoma
JAK3	<i>JAK3</i> , 19p13.11	JAK/STAT pathway, IL signaling pathway	CyclinD3, STAT3, STAT5, IL-2R, IL-6R, BCL2, IRF4, Myc, SHP-1	Nonreceptor tyrosine kinase	Involves in cell growth, development, and differentiation; mediates adaptive and innate immunity	Mutation	NK/T cell lymphoma, ATLL
MYD88	<i>MYD88</i> , 3p22.2	IL-1 signaling, TLR, NF- κ B pathway	TRAF6, TLR4, IL-1R1, NFKB2, IRAK2, IRAK4, CREBBP, EP300	Cytosolic adapter protein	Involves in innate and adaptive immunity	<i>MYD88</i> L256 mutation	LPL/WM, ABC-DLBCL, PCNSL
IL-6	<i>IL6</i> , 7p15.3	JAK/STAT, PI3K/AKT, and RAS/MAPK pathway	IL-6R, IL6ST	Pleiotropic cytokine	Functions in inflammation and B-cell maturation	Aberrant activation	B-NHL, Castleman's disease
PD-1	<i>PDCD1</i> , 2q37.3	Immune system pathway, TCR pathway	PD-L1, PD-L2, SHP-2,	Cell surface membrane protein of the immunoglobulin superfamily receptor	Negatively regulates effector T-cell functions	Overexpression in infiltrating T-cells	FL, CLL/SLL
PD-L1	<i>CD274</i> , 9p24.1	Immune system pathway, TCR pathway	PD-1	Immune inhibitory receptor ligand	Inhibits T-cell activation and cytokine production upon interaction with PD-1	Amplification, overexpression	cHL, PMBL, ABC-DLBCL, ALK+ALCL
PD-L2	<i>PDCD1LG2</i> , 9p24.1	Immune system pathway, TCR pathway	PD-1	Immune inhibitory receptor ligand	Inhibits T-cell activation and cytokine production upon interaction with PD-1	Amplification, overexpression	cHL

ABC, active B cell; AKT, v-akt murine thymoma viral oncogene homolog 1; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; BCR, B-cell receptor; BL, Burkitt lymphoma; BTK, bruton tyrosine kinase; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B cell; HL, Hodgkin lymphoma; IL-6, interleukin 6; JAK, Janus kinase; LPL, Lymphoplasmacytic Lymphoma; MALT, mucosa associated lymphoid tissue lymphoma; MCL, mantle cell lymphoma; MDM2, mouse double-minute 2 protein; mTOR, mechanistic target of Rapamycin; mTORC, mTOR complex; MYC, v-Myc avian myelocytomatosis viral oncogene homolog; MYD88, myeloid differentiation primary response 88; MZL, marginal zone lymphoma; NF- κ B, nuclear factor-kappaB; NHL, non-Hodgkin's lymphoma; PCNSL, primary central nervous system lymphoma; PD-1, programmed death-1; PD-Ls, programmed death-ligands; PI3K, phosphoinositide-3-kinase; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PKC β , protein kinase C β ; PMBL, primary mediastinal B-cell lymphoma; PTEN, phosphatase and tensin homolog; SHP, Src homology region 2 domain-containing phosphatase; SLL, small lymphocytic lymphoma; STAT, signal transducer and activator of transcription; SOCS, suppressor of cytokine signaling; SYK, spleen-associated tyrosine kinase; TCR, T-cell receptors; TLR, Toll-like receptors; WM, Waldenström's macroglobulinemia.

TABLE 2

Pathway-based oncogenic biomarkers and their therapeutic applications in lymphomas

Oncogenic Biomarker	Therapeutics	Agent	Involved Lymphomas	Phase	Trial Registration or Reference
BTK	Btk inhibitor	Ibrutinib (PCI-32765)	Recurrent B-cell lymphoma, CLL/SLL, R/R MCL, ABC-DLBCL, FL, MZL, T-cell lymphoma	Phase 1/2	NCT00849654; NCT01325701; NCT02169180; NCT01109069
	Btk inhibitor	BGB-3111	R/R B-cell malignancies	Phase 1	NCT02343120
	Btk inhibitor	AVL-292 (cc-292)	R/R B-Cell NHL, CLL/SLL, WM	Phase 1	NCT01351935
	Btk inhibitor	M7583	R/R B-cell malignancies, MCL, ABC-DLBCL	Phase 1/2	NCT02825836
SYK	Btk inhibitor	Acalabrutinib (ACP-196)	R/R ABC-DLBCL, CLL/SLL, MCL	Phase 1/2	NCT02112526; NCT02337829; NCT02029443; NCT02213926
	Syk inhibitor	Fostamatinib (R788) (R406)	CLL/SLL, DLBCL, MCL, FL, T-cell lymphoma	Phase 1/2	NCT004446095; NCT00798096
	Syk inhibitor	Cerdulatinib (PRT062070)	CLL/SLL, FL, NHL, T-cell lymphoma	Phase 1/2	NCT01994382
	Syk inhibitor	Entospletinib (GS-9973)	R/R CLL/SLL, MCL, DLBCL, FL; indolent NHL; MZL	Phase 2	NCT01799889
PI3Ks	PI3Kδ inhibitor	Idelalisib (CAL-101, GS-1101)	R/R MCL, FL, SLL, LPL, MZL	Phase 1/2	NCT00710528; NCT01282424
	PI3Kδ inhibitor	AMG 319	Lymphoid malignancies	Phase 1	NCT01300026
	PI3Kδ/γ inhibitor	Duvelisib (JPL-145, INK1197)	R/R NHL, advanced hematologic malignancies	Phase 1/2	NCT02598570; NCT01882803; NCT01476657
	PI3Kδ inhibitor	Acalisib (GS-9820) (CAL-120)	R/R lymphoid malignancy	Phase 1	NCT01705847
AKT	PI3Kγ inhibitor	Buparlisib (BKM120)	PCNSL, SCNSL, CLL/SLL	Phase 2	NCT02301364; NCT02340780
	PI3K inhibitor	SAR 245408 (XL147)	Lymphomas	Phase 1	NCT00486135
	Akt inhibitor	Perifosine (KRX-0401)	Hematologic malignancies, Lymphomas	Phase 1/2	NCT00019656; NCT00389077
	Akt1/2/3 inhibitor	MK-2206	Relapsed lymphoma, R/R DLBCL	Phase 2	NCT01258998; NCT01481129
mTOR	Akt inhibitor	GSK690693	Lymphoma and solid tumor	Phase 1	NCT00493818
	mTOR inhibitor	Ridaforolimus (AP23573, MK-8669)	Lymphoma, multiple myeloma, hematologic malignancies	Phase 2	NCT00060632; NCT00060645; NCT00086125
	mTOR inhibitor	Temsirolimus (CCI-779)	R/R HL, R/R PCNSL, FL, CLL/SLL, R/R MCL	Phase 1/2/4	NCT00838955; NCT00942747; NCT00033267; NCT01180049
	mTOR inhibitor	Rapamycin (Sirolimus)	R/R Acute Lymphoblastic Leukemia/Lymphoma	Terminated	NCT01658007
BCL2	mTORC1/mTORC2 inhibitor	Everolimus (RAD001)	R/R NHL, R/R MCL, R/R cutaneous T-cell lymphoma	Phase 1/2	NCT00622258; NCT00516412; NCT01637090
	mTORC1/mTORC2 inhibitor	AZD2014	R/R non-GCB DLBCL	Phase 1	NCT02780830
	Bcl-2, Bcl-xl, Bcl-w inhibitor	Navitoclax (ABT263)	R/R lymphoid malignancy	Phase 2	NCT00406809; NCT01557777
	BCL2 inhibitor	Venetoclax (ABT199)	NHL, CLL/SLL, MM, R/R NHL	Phase 1/2/3	NCT01969695; NCT01328626; NCT02756611; NCT02966756

Oncogenic Biomarker	Therapeutics	Agent	Involved Lymphomas	Phase	Trial Registration or Reference
p53	BCL2 inhibitor	Obatoclax Mesylate (GX15-070MS)	R/R HL	Phase 2	NCT00359892
	MDM2 inhibitor	APG-115	Advanced solid tumors or lymphomas	Phase 1	NCT02935907
	MDM2 inhibitor	DS-3032	Advanced solid tumors or lymphomas	Phase 1	NCT01877382
	P53-MDM2 blockade	ALRN-6924	Advanced solid tumors or lymphomas	Phase 1/2	NCT02264613
MYC	BET inhibitor	CPI-0610	Progressive lymphomas	Phase 1	NCT01949883; NCT02158858
	BET/BRD4 inhibitor	AZD5153	Hematologic malignancies	Preclinical	Reference ⁸⁶
	c-Myc-Max dimerization inhibitor	10058-F4	BL	Preclinical	Reference ⁸¹
	Aurora A inhibitor	Alisertib	Myc-positive aggressive B-cell lymphomas	Phase 1	NCT02700022
	Small inhibitory RNA oligonucleotide targeting MYC	DCR-MYC	NHL, MM, solid tumors	Phase 1	NCT02110563
	BET inhibitor	JQ1	Hematologic malignancies	Preclinical	Reference ⁸²⁻⁸⁴
JAKs	JAK3 inhibitor	Tofacitinib (CP-690550)	EBV-related NK/T-cell lymphoma	Preclinical	Reference ¹³²
	JAK2 inhibitor	Pacritinib (SB1518)	R/R cHL, FL, MCL, and DLBCL	Phase 1/2	NCT00741871; NCT01263899
	JAK2 inhibitor	Ruxolitinib (INCB018424)	R/R T-cell or NK-cell lymphoma, R/R HL and PMBL	Phase 2	NCT02974647; NCT01965119; NCT01877005
	STAT3 inhibitor	Pyrimethamine	Relapsed CLL/SLL	Phase 1/2	NCT01066663
STAT3	STAT3 inhibitor	IONIS-STAT3Rx (ISIS 481464)	DLBCL, lymphoma, advanced cancer	Phase 1/2	NCT01563302
IL-6	IL-6 inhibitor	Siltuximab (CNTO-328)	B-cell NHL, MM, or Castleman's disease	Phase 1	NCT00412321
PD-1	Anti-PD-1 antibody	MEDI0680 (AMP-514)	R/R aggressive B-cell lymphomas; advanced malignancies	Phase 1/2	NCT02271945; NCT02013804
	Anti-PD-1 antibody	Pidilizumab (CT-011)	DLBCL and PMBL after ASCT; stage III–IV DLBCL;	Phase 2	NCT00532259; NCT02530125
	Anti-PD-1 antibody	Nivolumab (BMS-936558, MDX-1106, ONO-4538)	R/R DLBCL, PCNSL, PTL, FL, PTCL	Phase 2	NCT02038933; NCT02857426; NCT02038946; NCT03075553
	Anti-PD-1 antibody	Pembrolizumab (lambrolizumab, MK-3475)	R/R FL; HL, DLBCL and T-NHL after ASCT; T-cell or NK-cell lymphomas; R/R HL; recurrent PCNSL; R/R PMBL	Phase 2	NCT02444647; NCT02362997; NCT03021057; NCT02453594; NCT02779101; NCT02576990
PD-L1	Anti-PD-L1 antibody	Durvalumab (MEDI4736)	R/R lymphoma, solid tumor	Phase 1	NCT02793466
	Anti-PD-L1 antibody	Avelumab (MSB0010718C)	Advanced cHL; R/R PTCL	Phase 1/2	NCT02603419; NCT03046953
	Anti-PD-L1 antibody	Atezolizumab (MPDL3280A) (RG7446)	Locally advanced or metastatic solid tumors or hematologic malignancies; R/R FL and DLBCL; R/R HL	Phase 1/2	NCT01375842; NCT02220842; NCT02862275; NCT03120676
MYD88	TLRs ligands inhibitor	IMO-8400	R/R ABC-DLBCL with MYD88 L256 mutation	Phase 1/2	NCT02252146
	IRAK4 inhibitor	ND-2158, ND-2110	ABC-DLBCL, or other malignancies harboring aberrant MYD88	Preclinical	Reference ¹³⁸
IkBa	IkBa inhibitor	Bortezomib (Velcade, PS341)	MALT, R/R FL, DLBCL, R/R B-cell lymphomas	Phase 2	NCT00210327; NCT00136591; NCT01226849; NCT00038571

Oncogenic Biomarker	Therapeutics	Agent	Involved Lymphomas	Phase	Trial Registration or Reference
	IkBa inhibitor	MLN4924	ABC-DLBCL, MCL, hematologic malignancies	Phase 1	NCT00722488

ABC, active B-cell; AKT, v-akt murine thymoma viral oncogene homolog1; ASCT, autologous stem cell transplantation; ATLL, Adult T-cell leukemia/lymphoma; BET, bromodomain and extra-terminal proteins; BRD4, bromodomain containing protein 4; BL, Burkitt lymphoma; BTK, bruton tyrosine kinase; cHL, classical Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; IL-6, interleukin 6; JAK, Janus kinase; LPL, lymphoplasmacytic lymphoma; MALT, mucosa associated lymphoid tissue lymphoma; MCL, mantle cell lymphoma; MDM2, mouse double-minute 2 protein; MM, multiple myeloma; mTOR, mechanistic target of Rapamycin; mTORC, mTOR complex; MYC, v-Myc avian myelocytomatosis viral oncogene homolog; MYD88, myeloid differentiation primary response 88; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; PCNSL, primary central nervous system lymphoma; PD-1, programmed death-1; PD-Ls, programmed death-ligands; PI3K, phosphoinositide-3-kinase; PMBL, primary mediastinal B-cell lymphoma; PTCL, peripheral T-cell lymphoma; R/R, refractory and relapsed; SCNSL, secondary central nervous system lymphoma; SLL, small lymphocytic lymphoma; STAT, signal transducer and activator of transcription; SYK, spleen-associated tyrosine kinase; WM, Waldenstrom's macroglobulinem.