Received: 28 May 2021 | Revised: 16 September 2021 | Accepted: 1 October 2021

DOI: 10.1002/hon.2933

REVIEW

WILEY

The resistance mechanisms and treatment strategies of BTK inhibitors in B-cell lymphoma

Haoran Wang[1] | Wentao Zhang[2] | Jingyi Yang[1] | Keshu Zhou[1]

[1]Department of Hematology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China

[2]Department of Urology, Armed Police Forces Hospital of Henan, Zhengzhou, China

Correspondence
Keshu Zhou and Jingyi Yang, Department of Hematology, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, No. 127, Dongming Road, Jinshui, Zhengzhou 450003, China.
Email: drzhouks77@163.com and zlyyyangjingyi4555@zzu.edu.cn

Funding information
National Natural Science Foundation of China, Grant/Award Number: 81470336

Abstract

Bruton's tyrosine kinase inhibitors (BTKi) have revolutionized the treatment of B-cell lymphoma (BCL). These drugs interfere with the mechanisms underlying malignant B-cell pathophysiology, allowing better drug response as well as low toxicity. However, these multiple mechanisms also lead to drug resistance, which compromised the treatment outcome and needs to be solved urgently. This review focuses on genomic variations (such as *BTK* and its downstream *PCLG2* mutations as well as Del 8p, 2p+, Del 6q/8p, *BIRC3*, *TRAF2*, *TRAF3*, *CARD11*, *MYD88*, and *CCND1* mutations) and related pathways (such as PI3K/Akt/mTOR, NF-κB, MAPK signaling pathways, overexpression of B-cell lymphoma 6, platelet-derived growth factor, toll-like receptors, and microenvironment, cancer stem cells, and exosomes) involved in cancer pathophysiology to discuss the mechanisms underlying resistance to BTKi. We have also reviewed the newly reported drug resistance mechanisms and the proposed potential treatment strategies (the next-generation BTKi, proteolysis-targeting chimera-BTK, XMU-MP-3, PI3K-Akt-mTOR pathway, MYC or LYN kinase inhibitor, and other small-molecule targeted drugs) to overcome drug resistance. The findings presented in this review lay a strong foundation for further research in this field.

KEYWORDS
B-cell lymphoma, BTK inhibitors, drug resistance, mutation, targeted drugs

1 | INTRODUCTION

Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase of TEC family and plays a crucial role in amplifying the B-cell antigen receptor (BCR) signaling pathway, which is indispensable for B-cell development and maturation.[1,2] Among the approaches available for targeting the BCR pathway, BTK inhibitors (BTKi) are regarded as promising and advanced therapeutic agents for B-cell lymphomas (BCL), including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), and Waldenström's macroglobulinemia (WM).[3] Ibrutinib, a first-generation BTKi, can block the downstream signaling of BCR by covalently binding to the BTK C481 residue (Figure 1).[4,5] As a first-line treatment for CLL/SLL, ibrutinib has demonstrated good safety profile and efficacy, especially in high-risk patients.[6] However, with the widespread use of targeted drugs, drug resistance has become a major problem. Although next-generation BTKi such as acalabrutinib, zanubrutinib, tirabrutinib, and orelabrutinib show greater BTK selectivity and less off-target toxicity, they cannot mitigate development of resistance to ibrutinib.[7] Therefore, research on the mechanisms underlying BTKi resistance and the selection of appropriate rescue treatments to achieve remission, especially minimal residual disease (MRD) negative, are of paramount importance.

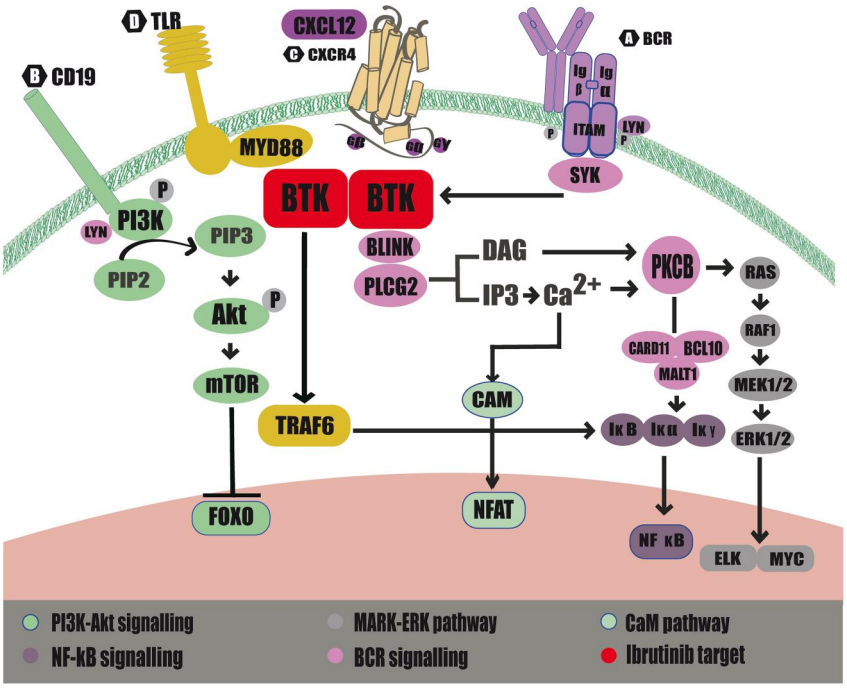

FIGURE 1 Bruton tyrosine kinase drives the cascade of B-cell antigen receptor signaling pathways, leading to the activation of downstream NF-κB, MAPK, and PI3K pro-survival pathways

2 | TREATMENT STATUS OF BTKi IN B-CELL LYMPHOMA

In a study of ibrutinib monotherapy for treatment-naïve (TN) or refractory (R/R) CLL/SLL patients, the overall response rate (ORR) was 87% for TN patients and 89% for R/R patients, and the five-year progression-free survival (PFS) rates were 92% and 44%, respectively.[8] These results suggested sustained efficacy and good tolerability of ibrutinib. In another study, poor prognostic factors such as del(11q), *TP53* mutation, and del(17p) were found not to influence the efficacy of ibrutinib.[9] Zanubrutinib also showed an ORR of 92.2% and 96% in TN and R/R CLL/SLL, respectively.[10,11] The clinical outcomes of BTKi in BCL are presented in Table 1.

However, despite exposure to targeted drugs, disease progression is inevitable in several cases. Among 202 CLL patients who received ibrutinib, 32% developed progressive disease, of which 15% developed Richter transformation (RT).[23] Among 97 R/R MCL patients treated with ibrutinib, 35% developed primary resistance, while 17.5% developed acquired resistance.[24] Clinical studies have shown that within four weeks of ibrutinib withdrawal, the condition of 25% patients deteriorated rapidly, and the median overall survival (OS) was only 2.9 months.[23,25,26] Thus, it is urgent to understand the mechanisms underlying BTKi resistance and seek better treatments.

3 | GENETIC MECHANISMS UNDERLYING BTKi RESISTANCE

Whole-exome sequencing showed that 80% of CLL patients with acquired resistance to ibrutinib harbor *BTK* and phospholipase C gamma 2 (*PLCG2*) mutations[27]; among them, the *BTK* C481S point mutation is the most common and imparts resistance by interfering with the reversible combination of ibrutinib and BTK protein. In addition, *BTK* mutations such as C481F/Y/R, T474I/S, L528W, T316A, and V537I were also observed in patients who developed ibrutinib resistance.[28] Estupinan et al.[29] confirmed that double mutations of BTK gatekeeper residues such as T474I/C481S, T474M/C481S, and T474M/C481T cause super resistance to ibrutinib, acalabrutinib, and zanubrutinib. *BTK* Leu528Trp mutation was also involved in zanubrutinib resistance.[30] S707Y, R665W, and L845F mutations in *PLCG2* had the effect of activating BCR-mediated downstream signaling independent of BTK.[31] Furthermore, Liu et al. reported that the activation of mutant PLCG2 protein was functionally dependent on LYN and SYK kinases. LYN, SYK, and PLCG2 formed a BTK bypass. Therefore, targeting LYN and SYK kinases could overcome ibrutinib resistance.[32] In addition, small duplicate deletions in the C2 terminal domain of *PLCG2* may also be related to BTKi resistance, and a reference for clinical resistance of unknown causes.[27,33]

In addition, there are other genomic variations related to BTKi resistance. Burger et al. found clonality of del(8p) in ibrutinib-resistant patients.[34] Although del(8p) clone declined slowly after initial ibrutinib treatment, it synergized with additional driver mutations, such as *EP300*, *EIF2A*, *SF3B1*, and *MLL2* to promote the tumor cell proliferation by providing a bypass signaling independent of BTK, and ultimately leading to ibrutinib resistance.[33,34] Tumor necrosis factor-related apoptosis-mediated ligand receptor (*TRAIL-R*) gene is in the 8p region and tumor apoptosis induced by TRAIL particularly depends on the dose of TRAIL-R.[35] The level of TRAIL-R protein decreased significantly in patients with del(8p)[27,34] Additionally, absence of TRAIL-R resulted in insensitivity to TRAIL-induced cell death.[34] When del(8p) CLL cells were released from

TABLE 1 Clinical outcomes of BTKi in B-cell lymphoma

Drug	B-cell lymphoma	Enrol patients	Status of disease	Clinical outcome	Reference
Ibrutinib	CLL/SLL	85	R/R	ORR:71%, PR:20%	12
		136	TN	ORR:92%, CR:30%	6
	MCL	111	R/R	ORR:68%, CR:21%	13
	WM	63	R/R	ORR:91%, MRR:73%	14
	ABC-DLBCL	38	R/R	ORR:37%	15
Acalabrutinib	CLL/SLL	61	R/R	ORR:95%	16
	MCL	124	R/R	ORR:81, PR:43%	17
Zanubrutinib	CLL/SLL	56	R/R	ORR:96%	11
		22	TN	ORR: 92.2%	11
	MCL	37	R/R	ORR:87%, CR:30%	18
		11	TN	ORR:88%, CR:38%	18
	WM	31	R/R	ORR:92%	19
Tirabrutinib	CLL/SLL	28	R/R	Objective response:96%	20
	MCL	16	R/R	ORR:92%, PR:54%	20
	WM	18	R/R	ORR:94%, MRR:89%	21
		9	TN	ORR:100%, MRR:89%	21
Orelabrutinib	CLL/SLL	80	R/R	ORR:93%, PR:65%	22

Abbreviations: ABC-DLBCL, activated B-cell-like diffuse large B-cell lymphoma; CLL, chronic lymphocytic leukemia; CR, complete response; MCL, mantle cell lymphoma; MRR, major response rate; ORR, objective response rate; PR, partial response; R/R, relapsed and refractory; TN, treatment naïve; WM, Waldenström's macroglobulinemia.

lymph node (LN) to peripheral blood (PB), they were highly insensitive to TRAIL, and subsequently caused unbridled tumor cell growth.[27] 2p+ was also related to a dismal outcome in CLL patients.[36] Moreover, the overexpression of exportin-1 (*XPO1*) could be induced by 2p+. Upregulation of XPO1 expression promoted tumor cell proliferation by regulating cytoplasmic localization and degrading tumor suppressor factors (such as FOXO and p53).[36,37] In MCL, the mutated BIRC3, TRAF2, and TRAF3 proteins activated the MP3K14 enzyme, which in turn activated the alternative NF-κB pathway, leading to uncontrolled cell growth and suppression of apoptosis[38,39] Mutations in the NF-κB pathway regulator, *CARD11*, were found in CLL, MCL, and WM patients who developed ibrutinib resistance.[40–42] Zhang et al.[43] found that the tumor cells derived from activated B cell-like DLBCL (ABC-DLBCL) patients who developed ibrutinib resistance carried the *MYD88* mutation and wild-type CD79A/B. Jimenez et al.[44] found a 6q or 8p homozygote deletion in WM patients with the *MYD88* L265P mutation. These patients received ibrutinib and experienced disease progression. However, the key negative regulators and apoptosis signals of BTK, MYD88, and NF-κB were located at 6q and 8p. In addition, they confirmed that ubiquitin ligase, toll-like receptor (TLR), and myeloid differentiation factor 88 (MYD88) pathway regulators are involved in ibrutinib resistance.[44,45] CXCR4 is a transmembrane chemokine receptor. After binding to CXCL12, it activates Akt and ERK pathways through the G protein to mediate lymphocyte migration and homing. Cao et al.[43,46] reported that *CXCR4* WHIM-like mutations were observed in 30% of WM patients, the most common of which was the *CXCR4 S338X* mutation. Compared with the CXCR4 wild-type protein, the mutant CXCR4 S338X protein could significantly activate Akt and ERK pathways, reduce cell apoptosis, and enhance cell viability. Mutation details of genes associated with BTKi resistance are presented in Table 2.

4 | DE-REGULATED PATHWAYS ASSOCIATED WITH BTKi RESISTANCE

4.1 | Signaling and kinase-related resistance mechanisms

More than 20% of ibrutinib-resistant patients do not carry any genetic variations, indicating that there are other mechanisms that allow tumor cells to partially adapt to BTKi. Following signaling and kinase-related resistance mechanisms have been proposed: (1) Activation of the PI3K pathway plays a crucial role in protecting mature B cells from apoptosis in the context of BCR deficiency.[47,48] Activated Akt protein together with deregulated phosphatase and tensin homolog deleted on chromosome 10 (PTEN) and forkhead box class O 3a (FOXO3a) proteins were observed in ibrutinib-resistant CLL, DLBCL, and MCL.[5] High expression of Akt directly phosphorylates

TABLE 2 Mutation details of genes associated with BTKi resistance

Gene	Mutation details
BTK	Kinase domain: C481S/F/Y/R, L528W, L512M, E513G, F517L, L547P, T474A/S/I in gatekeeper residue; double variants: T474I/C481S, T474M/C481S, T474M/C481T SH2 domain: T316A
PLCG2	Auto-inhibitory domain: Tyr495His SH2 domain: S707Y, R665W, L845F
BIRC3/TRAF2/TRAF3	BIRC3 E3 ligase domain: S441*, C560S TRAF2 exon 4: W114* Del TRAF3
CARD11	Coil-coiled (cc) domain: G123S, K215M, D230N, D357E Outside the cc domain: L878F
CCND1	Predominantly in exon 1 Repressor domain and Lxxll motify: E36K, Y44D and C47S

Note: * means nonsense mutation, Del means deletion of chromosome region.

Abbreviations: BTK, Bruton tyrosine kinase; BIRC3, baculoviral IAP repeat containing 3; CARD11, caspase recruitment domain 11; CCND1, cyclin D1; SH2 domain, Src Homology 2 domain; TRAF2, tumor necrosis factor receptor-associated factor.

downstream FOXO3a, leading to its sequestration and deregulation in the cytoplasm. Hence, less accumulation of FOXO3a in the nuclei activates the apoptosis-related genes *PTEN* and *BIM*.[49] However, the poor outcome of MCL patients was closely associated with phosphorylated cytoplasmic FOXO3a.[50] PTEN has the opposite function of PI3K; it can inhibit Akt activation and prevent signal transmission. The function of FOXO3a is mediated by nuclear translocation, which can be regulated by ibrutinib.[5] Therefore, exploring the FOXO3a/PTEN/Akt signaling pathway and its relationship with apoptosis in ibrutinib-resistant BCL is significant. (2) The activated mitogen-activated protein kinase (MAPK) pathway may also be a compensatory mechanism underlying BTKi resistance. A study reported that non-canonical NF-κB and MAPK pathway may be activated by CD40L-CD40 signaling independent of BTK signaling, and subsequently lead to ibrutinib resistance.[25,51,52] MYC is a transcription factor downstream of MAPK pathway, and its modulation is important in BCL development.[53] Compared with ibrutinib-resistant cell lines, MYC expression was suppressed in sensitive cell lines.[54] Additionally, *MYC* knockdown significant inhibited the growth of ibrutinib-resistant and sensitive cell lines. Therefore, upregulation of MYC expression may be involved in developing ibrutinib resistance. (3) Cell cycle defects: CCND1 mutations cause an increase in CCND1 protein levels through a proteolytic defect mechanism that leads to ibrutinib resistance.[55] (4) Upregulation of gene expression: *BCL6*, *IRF4*, *CD80*, and *PRDM1* are the common target genes of miR-30.[56] *BCL6* is overexpressed in patients who are unresponsive to ibrutinib. FX1 (a BCL6 inhibitor) can enhance the sensitivity of BTK C481S HBL-1 cells. Therefore, members of BCL6 and miR-30 families may be related to ibrutinib resistance in ABC-DLBCL. The expression of *PDGF* in patients with ibrutinib-resistant DLBCL was significantly upregulated than that in the sensitive group, whereas downregulated expression of *PDGF* could reverse ibrutinib resistance.[57] It is speculated that the abnormal expression of *PDGF* is related to BTKi resistance. In addition, *PDGF* can mediate ibrutinib resistance by upregulating the expression of *EGFR* in DLBCL.

4.2 | Tumor microenvironment-related resistance mechanisms

Tumor cell survival depends on the support of the surrounding tumor microenvironment (TME) that comprises stromal cells, cytokines, and growth factors, among other components.[58] Integrin β1 is the key molecule facilitating cell adhesion to the matrix. Zhao et al.[59] found that the integrin β1 receptor is overexpressed in MCL, and its stable knockdown in ibrutinib-resistant cells can significantly reduce cell adhesion, cell survival, and clonal growth. In addition, integrin β1 can regulate the activation of mTORC2-Akt signaling. Therefore, the mutual activation of phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-Akt-mTOR) and integrin β1 signal leads to the interaction between TME and lymphoma, which facilitates the growth of MCL cells and ibrutinib resistance.[59] Jayappa et al. found[60] that in CLL and MCL, treatment of cells with ibrutinib and venetoclax, after coculturing the tumor cells with TME agonists such as interleukin-10 (IL-10), CD40L, and CpG-ODNs (TLR-9 specific agonists), led to the activation of the NF-κB signaling pathway (especially alternative NF-κB). Subsequently, it induced the expression of the anti-apoptotic proteins MCL-1 and BCL-XL, and led to the development of resistance to the combination therapy.[60] As part of their payload, exosomes derived from CLL cells carry two proteins, S100-A9 and BAG-6. Compared with patients with indolent CLL, exosomes derived from advanced CLL patients showed elevated levels of S100-A9 and BAG-6 proteins, which promoted tumor escape and B-cell survival.[61,62] The non-malignant cells and matrix components in the TME play an important role in tumor cell survival, metastasis, and resistance. Guan et al.[63] reported that co-culture of

MS-5 stromal cells and Rec-1 or Mino MCL cell lines can significantly reduce the sensitivity of MCL cells to ibrutinib; moreover, after withdrawing ibrutinib, stromal cells can promote the regrowth of MCL cells. These results indicate that the interaction between stromal cells and MCL cells promotes drug resistance (Tables 3 and 4).

5 | POTENTIAL TREATMENT STRATEGIES FOR BTKi RESISTANCE

5.1 | Next-generation BTKi

To overcome BTKi resistance, several new non-covalent BTKi, such as LOXO-305, ARQ531, and XMU-MP-3 have been investigated. In a phase 1/2 study, the non-covalent third-generation BTKi, pirtobrutinib (LOXO-305), inhibited BTK kinase activity. It was used in CLL/SLL and MCL patients with BTKi resistance. LOXO-305 was well tolerated and the ORR was 62% in CLL and 52% in MCL patients.[64] ARQ531 is a potent, ATP-competitive, non-covalent inhibitor of BTK. It also could inhibits other kinases, such as LYN, ERK, and Akt, and does not interact with the BTK, C481.[65] A preclinical study showed that ARQ531 was an efficacious inhibitor of the downstream pro-survival PLCG2 signal transduction in ibrutinib-resistant mouse model.[65] XMU-MP-3 is a low-molecular-weight, non-covalent BTKi. It inhibited the BTK-mediated downstream pathway in ibrutinib-resistant mouse model with BTK C481S mutation and blocked phosphorylation of PLCγ2 in a dose-dependent manner.[28] In addition, fenebrutinib (GD-0853) and vecabrutinib are in the early stages of clinical testing, specifically for treating patients with BTK C481S mutation.

5.2 | BTK-PROATC

Proteolysis-targeting chimera (PROTAC)-induced degradation of BTK is highly selective and effective in a mouse model of the ibrutinib-resistant BTK C481S mutation.[66] PROTAC can use E3 ligase, such as pomalidomide and lenalidomide, as its binding partner to degrade its target proteins and exerts no obvious effects on other proteins such as ITK, EGFR, and TEC (off-targets of ibrutinib).[66] The BTK degrader, P13I (pomalidomide E3 ligase), induces significant degradation of wild-type C481S BTK proteins.[66] It is worth noting that the next-generation BTK degrader, L18I (lenalidomide E3 ligase), effectively degrades mutated BTK proteins and induces rapid tumor regression in BTK C481S xenograft model with lower toxicity. When combined with LYN, SYK, and the PI3K inhibitors, L18I exhibits even higher inhibitory activity.[67] However, BTK-PROTAC may not be able to mitigate BTK-independent ibrutinib resistance.[45]

TABLE 3 Genetic mechanisms underlying BTKi resistance and possible treatment strategies

Mutated gene	Disease	Mechanism	Possible treatment strategy	References
BTK	CLL, MCL, WM	Reversible binding BTKi	The third- generation BTKi, PROTAC-BTK, Bcl-2 inhibitor	28,30,64–67
PLCG2	CLL, MCL, WM	Independent of BTK downstream signal activation	LYN, SYK inhibitor	27,31,33,41
Del 8p	CLL	Loss of TRAIL-R and insensitivity to mediate apoptosis	Unknown	34,35
2p+	CLL	XPO1 overexpression	XPO1 inhibitor	36
BIRC3, TRAF2, DelTRAF3	MCL	Activation of NF-κB pathway	MP3K14 inhibitor	38,45
CARD11	DLBCL, CLL, MCL, WM	Compensatory activation of NF-κB pathway	MALT1 inhibitor	25,38,41,42,68
$MYD88^{mt}$ and $CD79A/B^{wt}$	DLBCL, WM	TLR signaling pathway	IRAK1/4 inhibitor	43,69–71
Del 6q	WM	MYD88/NFκB/BTK is up-regulated, and the apoptotic signal is missing	Unknown	44,45
Del 8p	WM	TLR/MYD88 overexpression	Unknown	44,45
CXCR4 (S338X)	WM	AKT and ERK activation	Unknown	43,46
CCND1	MCL	Cell cycle progression	Unknown	55,72

Abbreviations: BIRC3, baculoviral IAP repeat containing 3; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CARD11, caspase recruitment domain 11; CCND1, cyclin D1; CLL, chronic lymphocytic leukemia; CXCR4, C-X-C motif chemokine receptor 4; Del, means deletion of chromosome region; DLBCL, diffuse large B cell lymphoma; IRAK1/4, Interleukin-1 receptor-associated kinase 1/4; MALT1, Mucosa-associated lymphoid tissue lymphoma translocation gene 1; MCL, mantle cell lymphoma; MP3K14, mitogen-activated protein 3 kinase 14; PLCG2, phospholipase C gamma 2; PROTAC, Proteolysis Targeting Chimera; TLR, Toll-like receptor; TRAF2, tumor necrosis factor receptor-associated factor; TRAIL-R, tumor necrosis factor-related apoptosis-mediated ligand receptor; WM, Waldenström's macroglobulinemia; XPO1, recombinant exportin 1.

TABLE 4 De-regulated pathways associated with BTKi resistance and possible treatment strategies

Resistance mechanism	Disease	Possible treatment strategy	References
PI3K-Akt pathway activation	CLL, MCL, DLBCL	PI3K, mTOR or XPO1 inhibitor	5,46,73–75
MAPK pathway activation	CLL, MCL, DLBCL	MEK inhibitor, BET inhibitor	54,76
Up-regulation of MYC	MCL	HSP90 inhibitor	54,76,77
BCL6 overexpression	DLBCL	BCL6 inhibitor	56
PDGF overexpression	DLBCL	PDGF/EGFR inhibitor	57
TLR overexpression	CLL, DLBCL	IRAK1/4 inhibitor	69–71
Integrin β1 mediated adhesive protection	CLL, MCL	AVL4 inhibitor	59,78
Continuous proliferation of cancer stem cells	MCL	Wnt pathway inhibitor	79,80
Increased S100-A9 and BAG-6 proteins in exosomes	CLL	Unknown	61
Compensation pathway for energy metabolism	CLL	Fatty acid oxidation inhibitor (CTP1 inhibitor)	81,82
UPR (unfolded protein) low expression	DLBCL	2-DG	83

Abbreviations: 2-DG, 2-deoxy-D-glucose; AVL4, integrin very late antigen-4; BCL6, B-cell lymphoma 6; BET, bromodomain and extra-terminal; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; HSP90, heat shock proteins 90; IRAK1/4, Interleukin-1 receptor-associated kinase 1/4; MAPK, mitogen-activated protein kinase; MCL, mantle cell lymphoma; MEK, mitogen-activated ERK-regulating kinase; WM, Waldenström's macroglobulinemia; XPO1, recombinant exportin 1.

6 | THE THERAPEUTIC APPROACHES FOR ACQUIRED BTKi RESISTANCE

6.1 | PI3K-Akt-mTOR pathway

The PI3K-Akt-mTOR pathway plays an important role in ibrutinib-resistant CLL and ABC-DLBCL. The selective XPO1 inhibitor, selinexor, upregulates FOXO3a expression and acts against Akt to increase the apoptosis of ibrutinib-resistant cells. Additionally, selinexor mediated programmed cell death in CLL cells with del(17p) and unmutated *IGHV*, but had no effect on non-leukemic cells.[5,36] Jain et al. investigated the upregulated PI3K-Akt-mTOR pathway in ibrutinib-resistant DLBCL cell lines.[84] The PI3Kβ/δ dual inhibitor, KA2337, reduced the viability of ibrutinib-resistant cells and downregulated the PI3K-Akt-mTOR pathway. Additionally, the combination of KA2337 and chemotherapy drugs also enhanced the inhibitory effects on ibrutinib-resistant cells.[84] Paul et al.[73] found that PI3Kα and PI3Kδ are overexpressed in ABC-DLBCL, and both inhibitors can effectively inhibit the activity of the ibrutinib-resistant tumor cells in a mouse model. In a multicenter phase I/Ib study of ibrutinib combined with umbralisib (second-generation PI3K inhibitor) for treating R/R CLL and MCL, the ORR of R/R CLL and R/R MCL patients was 90% and 67%, respectively, and demonstrated good tolerability, greater response, and lower occurrence of Richter syndrome.[74]

6.2 | B-cell lymphoma 2 (BCL2) inhibitors

BCL2 is an important protein that regulates the apoptotic pathway. In recent years, the BCL2 inhibitor, venetoclax, has shown significant antitumor effects in BCL.[85] Kanagal-Shamanna et al. found that venetoclax can inhibit the tumor clones in CLL patients who developed resistance.[40] Furthermore, in a phase II study, treatment with a combination of ibrutinib and venetoclax showed encouraging results in R/R CLL and the ORR and CR rates were 89% and 51%, respectively. The undetectable minimal residual disease (uMRD) rates of PB and bone marrow (BM) were 53% and 36%, respectively. It is expected to reach the BM uMRD and even try to stop the drug.[86]

6.3 | Programmed cell death protein 1/programmed death-ligand 1 inhibitors

The programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1)pathway, an important immune checkpoint, plays a crucial role in the immune regulatory system. The upregulation of PD-L1 expression promotes immune escape in BCL.[87] Targeting PD-L1 reactivated immune function and prevented CLL development in Eμ-TCL1 mice.[88] In a phase 2 study with nine ibrutinib-resistant CLL patients, the ORR for pembrolizumab was 66%.[89] Additionally, in a clinical trial that evaluated the combined administration of nivolumab and ibrutinib to 23 patients with R/R CLL or RT (12 patients previously received BTKi), the ORR was 43%.[90] These results suggest that PD-1/PD-L1 inhibitors show good efficacy in BTKi resistant CLL or RT, and may be preferred therapeutic agents for these patients in the future.

6.4 | Kinase inhibitors

The HSP90 inhibitor, SNX-5422, mediates tumor cell apoptosis and downregulates MYC expression. SNX-5422 monotherapy reduced tumor burden and improved the OS of Eμ-TCL1 mice.[77] In preclinical

studies of BCL, voruciclib, a CDK inhibitor, reduced the phosphorylation of RNA pol II by inhibiting CDK9, thereby inhibiting the expression of MCL-1 and XIAP. Thus, the combination of voruciclib and venetoclax promotes apoptosis and inhibits tumor cell growth.[91–93] TG02 (zotiraciclib) is a multi-kinase (CDK1, 2, 5, 9) inhibitor and can inhibit the Lck and Fyn kinases (members of BCR signaling). Moreover, it blocks the BCR signaling, and inhibits the growth and proliferation of CLL cells.[93] Studies have confirmed that LYN and SYK kinases play crucial roles in BTK-bypass pathway. Thus, targeting LYN and SYK can block the activation of downstream signaling independent of BTK in ibrutinib-resistant cell lines.[32]

6.5 | MALT1 inhibitors

MALT1, a component of the CARD11-BCL10-MALT1 (CBM) complex, plays a crucial rule in BCR activation.[94] MALT-1 activity is upregulated in ABC-DLBCL and targeting MALT1 significantly inhibits the growth of ABC-DLBCL in vivo.[94] Another report from Saba et al. showed that MI-2 (MALT1 inhibitor) could inhibit the growth of CLL cells, indicating that it could be used to overcome BTKi resistance.[68]

6.6 | IRAK1/4 inhibitors

IRAK is a kinase that acts upstream of TLR signaling. Dadashian et al. reported that TLR signaling was upregulated in the LN of CLL patients compared with that in PB.[69] At the same time, the combination of ibrutinib and IRAK inhibitors could enhance the inhibitory effect of TLR signaling and mediate CLL cell apoptosis.[69,70] MYD88 is a key molecule involved in IRAK4 kinase-mediated activation of TLR signaling, and MYD88 L265P was found in 29% of ABC-DLBCL cases.[95] Another report indicated that the combination of ibrutinib and an IRAK inhibitor could inhibit the growth of MYD88 mutated DLBCL cell lines by blocking the NF-κB pathway.[71]

6.7 | Other small molecule targeted drugs

In recent years, inhibition of the bromodomain extra-terminal (BET) protein has emerged as a promising option for BCL treatment by attenuating disease-relevant gene expression such as *MYC* and *NF-κB*.[96] The BET inhibitor, GS-5829, can inhibit the key signaling pathways of BLK, Akt, ERK1/2, and MYC, thereby inhibiting CLL cell proliferation and inducing tumor cell apoptosis.[76] Additionally, BET proteins targeting PROTAC have shown notable inhibitory effects in xenograft mouse models of ABC-DLBCL and ibrutinib-resistant MCL.[97,98] The survival and homing of tumor cells greatly depend on the BCR pathway and integrin-mediated adhesion. Integrin very late antigen-4 (VLA-4) inhibitors can suppress BCR signaling and cell adhesion, which is a potential therapeutic method.[78] Previous studies have shown that ibrutinib interferes with BCR signaling by inhibiting fatty acid synthesis.[81] The redox balance shifted to nicotinamide adenine dinucleotide phosphate in ibrutinib-resistant CLL cells, but glutamine uptake did not increase, confirming the existence of an alternative energy metabolism process, that is, fatty acid oxidation. Carnitine palmitoyltransferase 1 (CPT1) inhibitors can reverse BTKi resistance by inhibiting the oxidation of fatty acids.[82] 2-deoxy-D-glucose (2-DG) activates the unfolded protein response (UPR) in cells. Studies have confirmed that UPR expression is significantly lower in DLBCL ibrutinib-resistant cell lines. Moreover, the combination of 2-DG with ibrutinib significantly reduced tumor cell growth in a xenograft model.[83]

6.8 | Target cancer stem cells

Cancer stem cells (CSCs) rely on Wnt, Notch, and other signaling pathways for self-renewal.[99] However, little is known about CSC biology and effective therapy regimen for BCL. Mathur et al. found that in MCL-derived CSCs, the Wnt pathway is upregulated and these CSCs are resistant to ibrutinib[79]; therefore, targeting the Wnt pathway may be an option to overcome resistance. Wnt inhibitors such as iCRT14 can eliminate MCL-initiating cells by blocking the β-catenin-TCF4 transcription complex and further blocking the Wnt pathway.[79]

6.9 | BTKi in combination with CD20 immunotherapy

Although targeted drugs have become mainstay of BCL treatment, a combination therapeutic regimen including immunotherapy is a promising option to solve targeted drug resistance. Anti-CD20 monoclonal antibody kills tumor cells through complement-dependent cytotoxicity (CDC), antibody-dependent cytotoxicity (ADCC), antibody-mediated phagocytosis, and inducing apoptosis.[100] A multi-center phase II study showed that the remission rate of ublituximab combined with ibrutinib in R/R CLL patients reached 88%; in patients with high-risk cytogenetic factors, the remission rate reached 95%, and 15% of patients were MRD negative.[101]

6.10 | Chimeric antigen receptor T cell with BTKi for combination therapy

As a research hotspot in recent years, chimeric antigen receptor T cell (CAR-T) has attracted much attention for hematological tumors. Results from the ZUMA-1 study showed that the complete response rate of R/R DLBCL patients reached 59%, and the ORR reached 83%, which was nearly 12-fold higher than that of standard-of-care therapy (7%).[102,103] In a phase II study of KTE-X19, the ORR of R/R MCL patients was 93%, CR rate reached 67%, and MRD negative rate at 4 weeks reached 83%,[104] thus showing promising results. In a study combining CAR-T with ibrutinib to treat 19 R/R CLL patients in which

ibrutinib treatment failed, the ORR and BM uMRD rates were 83% and 61%, respectively.[105] In addition, acalabrutinib in combination with CD19 CAR-T enhanced CAR-T therapy response in BCL.[87]

7 | SUMMARY AND OUTLOOK

With the development of genomic sequencing and immunotherapy, the treatment of BCL has entered the era of precision therapy.[106] More analysis from the real world is needed to solve the problem of drug resistance. Apart from the above-discussed potential treatment strategies, some potential combination therapies such as BTKi in combination with compensation pathway inhibitors (PI3K, IRAK4, XPO1, MP3K14 inhibitors), and BCL2 inhibitors are other potential therapeutic modalities. In addition, the use of CAR-T and PD1/PD-L1 inhibitors in combination with BTKi is a promising approach. Scientific researchers and clinicians should use the latest detection technologies to track the effects of preclinical and therapeutic drugs in a timely manner and select appropriate new drugs and targeted combination treatments.

ACKNOWLEDGMENTS

This work was funded by the National Natural Science Foundation of China (81470336).

CONFLICT OF INTERESTS

All authors declare no conflict of interest.

ETHICS STATEMENT

Being a review article, ethical committee approval was not required.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Haoran Wang https://orcid.org/0000-0003-3948-2863
Keshu Zhou https://orcid.org/0000-0001-5467-1377

TRANSPARENT PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/hon.2933.

REFERENCES

1. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer*. 2018;17(1):57. doi:10.1186/s12943-018-0779-z
2. Wang X, Kokabee L, Kokabee M, Conklin DS. Bruton's tyrosine kinase and its isoforms in cancer. *Front Cell Dev Biol*. 2021;9:668996. doi:10.3389/fcell.2021.668996
3. Ahn IE, Brown JR. Targeting Bruton's tyrosine kinase in CLL. *Front Immunol*. 2021;12:687458. doi:10.3389/fimmu.2021.687458
4. Sivina M, Kreitman RJ, Arons E, Ravandi F, Burger JA. The bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) blocks hairy cell leukaemia survival, proliferation and B cell receptor signalling: a new therapeutic approach. *Br J Haematol*. Jul. 2014;166(2):177-188. doi:10.1111/bjh.12867
5. Kapoor I, Li Y, Sharma A, et al. Resistance to BTK inhibition by ibrutinib can be overcome by preventing FOXO3a nuclear export and PI3K/AKT activation in B-cell lymphoid malignancies. *Cell Death Dis*. 2019;10(12):924. doi:10.1038/s41419-019-2158-0
6. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34(3):787-798. doi:10.1038/s41375-019-0602-x
7. Bond DA, Woyach JA. Targeting BTK in CLL: beyond ibrutinib. *Curr Hematol Malig Rep*. 2019;14(3):197-205. doi:10.1007/s11899-019-00512-0
8. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood*. 2018;131(17):1910-1919. doi:10.1182/blood-2017-10-810044
9. Gribben JG, Bosch F, Cymbalista F, et al. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. *Br J Haematol*. 2018;180(5):666-679. doi:10.1111/bjh.15080
10. Xu W, Yang S, Zhou K, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study. *J Hematol Oncol*. 2020;13(1):48. doi:10.1186/s13045-020-00884-4
11. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood*. 2019;134(11):851-859. doi:10.1182/blood.2019001160
12. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013;369(1):32-42. doi:10.1056/NEJMoa1215637
13. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739-745. doi:10.1182/blood-2015-03-635326
14. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med*. 2015;372(15):1430-1440. doi:10.1056/NEJMoa1501548
15. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med*. 2015;21(8):922-926. doi:10.1038/nm.3884
16. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):323-332. doi:10.1056/NEJMoa1509981
17. Wang M, Rule S, Zinzani PL, et al. Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. *Leukemia*. 2019;33(11):2762-2766. doi:10.1038/s41375-019-0575-9
18. Tam CS, Wang M, Simpson D, et al. Updated safety and efficacy data in the phase 1 trial of patients with mantle cell lymphoma (MCL) treated with Bruton tyrosine kinase (BTK) inhibitor zanubrutinib (Bgb-3111). *Hematol Oncol*. 2019;37(S2):245-247. doi:10.1002/hon.55_2630
19. Tam CS, Trotman J, Opat S, et al. High major response rate, including very good partial responses (VGPR), in patients (pts) with Waldenstrom macroglobulinemia (WM) treated with the highly specific BTK inhibitor Bgb-3111: expansion phase results from an ongoing phase I study. *Blood*. 2016;128(22):1216. doi:10.1182/blood.V128.22.1216.1216
20. Walter HS, Rule SA, Dyer MJ, et al. A phase 1 clinical trial of the selective BTK inhibitor ONO/GS-4059 in relapsed and refractory mature B-cell malignancies. *Blood*. 2016;127(4):411-419. doi:10.1182/blood-2015-08-664086

21. Sekiguchi N, Rai S, Munakata W, et al. A multicenter, open-label, phase II study of tirabrutinib (ONO/GS-4059) in patients with Waldenstrom's macroglobulinemia. *Cancer Sci*. 2020;111(9):3327-3337. doi:10.1111/cas.14561
22. Xu W, Song Y, Wang T, et al. Updated efficacy and safety results of orelabrutinib in the treatment of relapsed or refractory chronic lymphocytic leukemia/small cell leukemia. *Hematol Oncol*. 2021;39(S2). doi:10.1002/hon.43_2880
23. Hampel PJ, Ding W, Call TG, et al. Rapid disease progression following discontinuation of ibrutinib in patients with chronic lymphocytic leukemia treated in routine clinical practice. *Leuk Lymphoma*. 2019;60(11):2712-2719. doi:10.1080/10428194.2019.1602268
24. Epperla N, Hamadani M, Cashen AF, et al. Predictive factors and outcomes for ibrutinib therapy in relapsed/refractory mantle cell lymphoma-a "real world" study. *Hematol Oncol*. 2017;35(4):528-535. doi:10.1002/hon.2380
25. Hershkovitz-Rokah O, Pulver D, Lenz G, Shpilberg O. Ibrutinib resistance in mantle cell lymphoma: clinical, molecular and treatment aspects. *Br J Haematol*. 2018;181(3):306-319. doi:10.1111/bjh.15108
26. Martin P. Ibrutinib -- a new standard treatment for relapsed mantle cell lymphoma? *Lancet*. 2016;387(10020):728-729. doi:10.1016/S0140-6736(15)01040-5
27. Zhou H, Hu P, Yan X, Zhang Y, Shi W. Ibrutinib in chronic lymphocytic leukemia: clinical applications, drug resistance, and prospects. *Onco Targets Ther*. 2020;13:4877-4892. doi:10.2147/OTT.S249586
28. Gui F, Jiang J, He Z, et al. A non-covalent inhibitor XMU-MP-3 overrides ibrutinib-resistant Btk(C481S) mutation in B-cell malignancies. *Br J Pharmacol*. 2019;176(23):4491-4509. doi:10.1111/bph.14809
29. Estupinan HY, Wang Q, Berglof A, et al. BTK gatekeeper residue variation combined with cysteine 481 substitution causes superresistance to irreversible inhibitors acalabrutinib, ibrutinib and zanubrutinib. *Leukemia*. 2021;35:1317-1329. doi:10.1038/s41375-021-01123-6
30. Handu Nn Etti SM, Tang C, Nguyen T, et al. BTK Leu528Trp – a potential secondary resistance mechanism specific for patients with chronic lymphocytic leukemia treated with the next generation BTK inhibitor zanubrutinib. *Blood*. 2019;134(Suppl_1):170-170. doi:10.1182/blood-2019-125488
31. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370(24):2286-2294. doi:10.1056/NEJMoa1400029
32. Liu TM, Woyach JA, Zhong Y, et al. Hypermorphic mutation of phospholipase C, gamma2 acquired in ibrutinib-resistant CLL confers BTK independency upon B-cell receptor activation. *Blood*. 2015;126(1):61-68. doi:10.1182/blood-2015-02-626846
33. Landau DA, Sun C, Rosebrock D, et al. The evolutionary landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy. *Nat Commun*. 2017;8(1):2185. doi:10.1038/s41467-017-02329-y
34. Burger JA, Landau DA, Taylor-Weiner A, et al. Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. *Nat Commun*. 2016;7:11589. doi:10.1080/10428194.2019.1602268
35. Rubio-Moscardo F, Blesa D, Mestre C, et al. Characterization of 8p21.3 chromosomal deletions in B-cell lymphoma: TRAIL-R1 and TRAIL-R2 as candidate dosage-dependent tumor suppressor genes. *Blood*. 2005;106(9):3214-3222. doi:10.1182/blood-2005-05-2013
36. Cosson A, Chapiro E, Bougacha N, et al. Gain in the short arm of chromosome 2 (2p+) induces gene overexpression and drug resistance in chronic lymphocytic leukemia: analysis of the central role of XPO1. *Leukemia*. 2017;31(7):1625-1629. doi:10.1038/leu.2017.100
37. Senapedis WT, Baloglu E, Landesman Y. Clinical translation of nuclear export inhibitors in cancer. *Semin Cancer Biol*. 2014;27:74-86. doi:10.1016/j.semcancer.2014.04.005
38. Rahal R, Frick M, Romero R, et al. Pharmacological and genomic profiling identifies NF-kappa B-targeted treatment strategies for mantle cell lymphoma. *Nat Med*. 2014;20(1):87-92. doi:10.1038/nm.3435
39. Vallabhapurapu S, Matsuzawa A, Zhang W, et al. Nonredundant and complementary functions of TRAF2 and TRAF3 in a ubiquitination cascade that activates NIK-dependent alternative NF-kappaB signaling. *Nat Immunol*. 2008;9(12):1364-1370. doi:10.1038/ni.1678
40. Kanagal-Shamanna R, Jain P, Patel KP, et al. Targeted multigene deep sequencing of Bruton tyrosine kinase inhibitor-resistant chronic lymphocytic leukemia with disease progression and Richter transformation. *Cancer*. 2019;125(4):559-574. doi:10.1002/cncr.31831
41. Xu L, Tsakmaklis N, Yang G, et al. Acquired mutations associated with ibrutinib resistance in Waldenstrom macroglobulinemia. *Blood*. 2017;129(18):2519-2525. doi:10.1182/blood-2017-01-761726
42. Wu C, de Miranda NF, Chen L, et al. Genetic heterogeneity in primary and relapsed mantle cell lymphomas: impact of recurrent CARD11 mutations. *Oncotarget*. 2016;7(25):38180-38190. doi:10.18632/oncotarget.9500
43. Zhang SQ, Smith SM, Zhang SY, Lynn Wang Y. Mechanisms of ibrutinib resistance in chronic lymphocytic leukaemia and non-Hodgkin lymphoma. *Br J Haematol*. 2015;170(4):445-456. doi:10.1111/bjh.13427
44. Jimenez C, Chan GG, Xu L, et al. Genomic evolution of ibrutinib-resistant clones in Waldenstrom macroglobulinaemia. *Br J Haematol*. 2020;189(6):1165-1170. doi:10.1111/bjh.16463
45. George B, Chowdhury SM, Hart A, et al. Ibrutinib resistance mechanisms and treatment strategies for B-cell lymphomas. *Cancers*. 2020;12(5):1328. doi:10.3390/cancers12051328
46. Cao Y, Hunter ZR, Liu X, et al. The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom's macroglobulinemia. *Leukemia*. 2015;29(1):169-176. doi:10.1038/leu.2014.187
47. Lam KP, Kuhn R, Rajewsky K. In vivo ablation of surface immunoglobulin on mature B cells by inducible gene targeting results in rapid cell death. *Cell*. 1997;90(6):1073-1083. doi:10.1016/s0092-8674(00)80373-6
48. Srinivasan L, Sasaki Y, Calado DP, et al. PI3 kinase signals BCR-dependent mature B cell survival. *Cell*. 2009;139(3):573-586. doi:10.1016/j.cell.2009.08.041
49. Xie M, Yang A, Ma J, et al. Akt2 mediates glucocorticoid resistance in lymphoid malignancies through FoxO3a/Bim axis and serves as a direct target for resistance reversal. *Cell Death Dis*. 2019;9(10):1013. doi:10.1038/s41419-018-1043-6
50. Obrador-Hevia A, Serra-Sitjar M, Rodriguez J, Villalonga P, Fernandez de Mattos S. The tumour suppressor FOXO3 is a key regulator of mantle cell lymphoma proliferation and survival. *Br J Haematol*. 2012;156(3):334-345. doi:10.1111/j.1365-2141.2011.08951.x
51. Sun Z, Luo L. Abstract 1298: CD40L-CD40 signaling on B-cell lymphoma response to BTK inhibitors. *Cancer Res*. 2016;76(14 Supplement):1298. doi:10.1158/1538-7445.AM2016-1298
52. Rauert-Wunderlich H, Rudelius M, Berberich I, Rosenwald A. CD40L mediated alternative NFkappa B-signaling induces resistance to BCR-inhibitors in patients with mantle cell lymphoma. *Cell Death Dis*. 2018;9(2):86. doi:10.1038/s41419-017-0157-6

53. Delgado MD, Leon J. Myc roles in hematopoiesis and leukemia. *Genes Cancer*. 2010;1(6):605-616. doi:10.1177/1947601910377495
54. Lee J, Zhang LL, Wu W, et al. Activation of MYC, a bonafide client of HSP90, contributes to intrinsic ibrutinib resistance in mantle cell lymphoma. *Blood Adv*. 2018;2(16):2039-2051. doi:10.1182/bloodadvances.2018016048
55. Mohanty A, Sandoval N, Das M, et al. CCND1 mutations increase protein stability and promote ibrutinib resistance in mantle cell lymphoma. *Oncotarget*. 2016;7(45):73558-73572. doi:10.18632/oncotarget.12434
56. Li J, Huang Y, Zhang Y, et al. Identification BCL6 and miR-30 family associating with ibrutinib resistance in activated B-cell-like diffuse large B-cell lymphoma. *Med Oncol*. 2021;38(4):33. doi:10.1007/s12032-021-01470-5
57. Jin J, Wang L, Tao Z, et al. PDGFD induces ibrutinib resistance of diffuse large B cell lymphoma through activation of EGFR. *Mol Med Rep*. 2020;21(5):2209-2219. doi:10.3892/mmr.2020.11022
58. Nguyen PH, Fedorchenko O, Rosen N, et al. LYN kinase in the tumor microenvironment is essential for the progression of chronic lymphocytic leukemia. *Cancer Cell*. 2016;30(4):610-622. doi:10.1016/j.ccell.2016.09.007
59. Zhao X, Lwin T, Silva A, et al. Unification of de novo and acquired ibrutinib resistance in mantle cell lymphoma. *Nat Commun*. 2017;8:14920. doi:10.1038/ncomms14920
60. Jayappa KD, Portell CA, Gordon VL, et al. Microenvironmental agonists generate de novo phenotypic resistance to combined ibrutinib plus venetoclax in CLL and MCL. *Blood Adv*. 2017;1(14):933-946. doi:10.1182/bloodadvances.2016004176
61. Nisticò N, Maisano D, Iaccino E, et al. Role of chronic lymphocytic leukemia (CLL)-derived exosomes in tumor progression and survival. *Pharmaceuticals*. 2020;13(9):244. doi:10.3390/ph13090244
62. Reiners KS, Topolar D, Henke A, et al. Soluble ligands for NK cell receptors promote evasion of chronic lymphocytic leukemia cells from NK cell anti-tumor activity. *Blood*. 2013;121(18):3658-3665. doi:10.1182/blood-2013-01-476606
63. Guan J, Huang D, Yakimchuk K, Okret S. p110alpha inhibition overcomes stromal cell-mediated ibrutinib resistance in mantle cell lymphoma. *Mol Cancer Ther*. 2018;17(5):1090-1100. doi:10.1158/1535-7163.MCT-17-0784
64. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397(10277):892-901. doi:10.1016/S0140-6736(21)00224-5
65. Reiff SD, Mantel R, Smith LL, et al. The BTK inhibitor ARQ 531 targets ibrutinib-resistant CLL and Richter transformation. *Cancer Discov*. 2018;8(10):1300-1315. doi:10.1158/2159-8290.CD-17-1409
66. Sun Y, Zhao X, Ding N, et al. PROTAC-induced BTK degradation as a novel therapy for mutated BTK C481S induced ibrutinib-resistant B-cell malignancies. *Cell Res*. 2018;28(7):779-781. doi:10.1038/s41422-018-0055-1
67. Sun Y, Ding N, Song Y, et al. Degradation of Bruton's tyrosine kinase mutants by PROTACs for potential treatment of ibrutinib-resistant non-Hodgkin lymphomas. *Leukemia*. 2019;33(8):2105-2110. doi:10.1038/s41375-019-0440-x
68. Saba NS, Wong DH, Tanios G, et al. MALT1 inhibition is efficacious in both naive and ibrutinib-resistant chronic lymphocytic leukemia. *Cancer Res*. 2017;77(24):7038-7048. doi:10.1158/0008-5472.CAN-17-2485
69. Dadashian EL, McAuley EM, Liu D, et al. TLR signaling is activated in lymph node-resident CLL cells and is only partially inhibited by ibrutinib. *Cancer Res*. 2019;79(2):360-371. doi:10.1158/0008-5472.CAN-18-0781
70. Delvecchio VS, Sana I, Mantione ME, et al. Interleukin-1 receptor-associated kinase 4 inhibitor interrupts toll-like receptor signalling and sensitizes chronic lymphocytic leukaemia cells to apoptosis. *Br J Haematol*. 2020;189(3):475-488. doi:10.1111/bjh.16386
71. Chen Y, Bai G, Ning Y, et al. Design and synthesis of Imidazo [1,2-b]pyridazine IRAK4 inhibitors for the treatment of mutant MYD88 L265P diffuse large B-cell lymphoma. *Eur J Med Chem*. 2020;190:112092. doi:10.1016/j.ejmech.2020.112092
72. Bea S, Valdes-Mas R, Navarro A, et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. *Proc Natl Acad Sci U S A*. 2013;110(45):18250-18255. doi:10.1073/pnas.1314608110
73. Paul J, Soujon M, Wengner AM, et al. Simultaneous inhibition of PI3Kdelta and PI3Kalpha induces ABC-DLBCL regression by blocking BCR-dependent and -independent activation of NF-kappaB and AKT. *Cancer Cell*. 2017;31(1):64-78. doi:10.1016/j.ccell.2016.12.003
74. Davids MS, Kim HT, Nicotra A, et al. Umbralisib in combination with ibrutinib in patients with relapsed or refractory chronic lymphocytic leukaemia or mantle cell lymphoma: a multicentre phase 1-1b study. *Lancet Haematol*. 2019;6(1):e38-e47. doi:10.1016/S2352-3026(18)30196-0
75. Ondrisova L, Mraz M. Genetic and non-genetic mechanisms of resistance to BCR signaling inhibitors in B cell malignancies. *Front Oncol*. 2020;10:591577. doi:10.3389/fonc.2020.591577
76. Kim E, Ten Hacken E, Sivina M, et al. The BET inhibitor GS-5829 targets chronic lymphocytic leukemia cells and their supportive microenvironment. *Leukemia*. 2020;34(6):1588-1598. doi:10.1038/s41375-019-0682-7
77. Chen TL, Harrington B, Truxall J, et al. Preclinical evaluation of the Hsp90 inhibitor SNX-5422 in ibrutinib resistant CLL. *J Hematol Oncol*. 2021;14(1):36. doi:10.1186/s13045-021-01039-9
78. Harzschel A, Zucchetto A, Gattei V, Hartmann TN. VLA-4 expression and activation in B cell malignancies: functional and clinical aspects. *Int J Mol Sci*. 2020;21(6):2206. doi:10.3390/ijms21062206
79. Mathur R, Sehgal L, Braun FK, et al. Targeting Wnt pathway in mantle cell lymphoma-initiating cells. *J Hematol Oncol*. 2015;8:63. doi:10.1186/s13045-015-0161-1
80. Wei X, Yang S, Pu X, et al. Tumor-associated macrophages increase the proportion of cancer stem cells in lymphoma by secreting pleiotrophin. *Am J Transl Res*. 2019;11(10):6393-6402.
81. Rozovski U, Harris DM, Li P, et al. Ibrutinib inhibits free fatty acid metabolism in chronic lymphocytic leukemia. *Leuk Lymphoma*. 2018;59(11):2686-2691. doi:10.1080/10428194.2018.1439167
82. Galicia-Vazquez G, Aloyz R. Ibrutinib resistance is reduced by an inhibitor of fatty acid oxidation in primary CLL lymphocytes. *Front Oncol*. 2018;8:411. doi:10.3389/fonc.2018.00411
83. Zhang XT, Hu XB, Wang HL, et al. Activation of unfolded protein response overcomes ibrutinib resistance in diffuse large B-cell lymphoma. *Acta Pharmacol Sin*. 2020;42:814-823. doi:10.1038/s41401-020-00505-3
84. Jain N, Havranek O, Singh RK, et al. Overcoming ibrutinib resistance by targeting phosphatidylinositol-3-kinase signaling in diffuse large B-cell lymphoma. *BioRXIV*. 2019. doi:10.1101/523761
85. Vandenberg CJ, Cory S. ABT-199, a new Bcl-2-specific BH3 mimetic, has in vivo efficacy against aggressive Myc-driven mouse lymphomas without provoking thrombocytopenia. *Blood*. 2013;121(12):2285-2288. doi:10.1182/blood-2013-01-475855
86. Hillmen P, Rawstron AC, Brock K, et al. Ibrutinib plus venetoclax in relapsed/refractory chronic lymphocytic leukemia: the CLARITY Study. *J Clin Oncol*. 2019;37(30):2722-2729. doi:10.1200/JCO.19.00894
87. Qin JS, Johnstone TG, Baturevych A, et al. Antitumor potency of an anti-CD19 chimeric antigen receptor T-cell therapy, lisocabtagene maraleucel in combination with ibrutinib or acalabrutinib. *J*

Immunother. 2020;43(4):107-120. doi:10.1097/CJI.0000000000000307
88. McClanahan F, Hanna B, Miller S, et al. PD-L1 checkpoint blockade prevents immune dysfunction and leukemia development in a mouse model of chronic lymphocytic leukemia. *Blood*. 2015;126(2):203-211. doi:10.1182/blood-2015-01-622936
89. Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood*. 2017;129(26):3419-3427. doi:10.1182/blood-2017-02-765685
90. Jain N, Ferrajoli A, Basu S, et al. A phase II trial of nivolumab combined with ibrutinib for patients with Richter transformation. *Blood*. 2018;132(Suppl 1):296. doi:10.1182/blood-2018-99-120355
91. Luedtke DA, Su Y, Ma J, et al. Inhibition of CDK9 by voruciclib synergistically enhances cell death induced by the Bcl-2 selective inhibitor venetoclax in preclinical models of acute myeloid leukemia. *Signal Transduct Target Ther*. 2020;5(1):17. doi:10.1038/s41392-020-0112-3
92. Dey J, Deckwerth TL, Kerwin WS, et al. Voruciclib, a clinical stage oral CDK9 inhibitor, represses MCL-1 and sensitizes high-risk diffuse large B-cell lymphoma to BCL2 inhibition. *Sci Rep*. 2017;7(1):18007. doi:10.1038/s41598-017-18368-w
93. Chen R, Tsai J, Thompson PA, et al. The multi-kinase inhibitor TG02 induces apoptosis and blocks B-cell receptor signaling in chronic lymphocytic leukemia through dual mechanisms of action. *Blood Cancer J*. 2021;11(3):57. doi:10.1038/s41408-021-00436-0
94. Fontan L, Qiao Q, Hatcher JM, et al. Specific covalent inhibition of MALT1 paracaspase suppresses B cell lymphoma growth. *J Clin Invest*. 2018;128(10):4397-4412. doi:10.1172/JCI99436
95. Kelly PN, Romero DL, Yang Y, et al. Selective interleukin-1 receptor-associated kinase 4 inhibitors for the treatment of autoimmune disorders and lymphoid malignancy. *J Exp Med*. 2015;212(13):2189-2201. doi:10.1084/jem.20151074
96. Albrecht BK, Gehling VS, Hewitt MC, et al. Identification of a benzoisoxazoloazepine inhibitor (CPI-0610) of the bromodomain and extra-terminal (BET) family as a candidate for human clinical trials. *J Med Chem*. 2016;59(4):1330-1339. doi:10.1021/acs.jmedchem.5b01882
97. Sun B, Fiskus W, Qian Y, et al. BET protein proteolysis targeting chimera (PROTAC) exerts potent lethal activity against mantle cell lymphoma cells. *Leukemia*. 2018;32(2):343-352. doi:10.1038/leu.2017.207
98. Jain N, Hartert K, Tadros S, et al. Targetable genetic alterations of TCF4 (E2-2) drive immunoglobulin expression in diffuse large B cell lymphoma. *Sci Transl Med*. 2019;11(497):eaav5599. doi:10.1126/scitranslmed.aav5599
99. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature*. 2001;414(6859):105-111. doi:10.1038/35102167
100. Cavallini C, Galasso M, Pozza ED, et al. Effects of CD20 antibodies and kinase inhibitors on B-cell receptor signalling and survival of chronic lymphocytic leukaemia cells. *Br J Haematol*. 2021;192(2):333-342. doi:10.1111/bjh.17139
101. Sharman JP, Farber CM, Mahadevan D, et al. Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial. *Br J Haematol*. 2017;176(3):412-420. doi:10.1111/bjh.14447
102. 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
103. 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
104. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382(14):1331-1342. doi:10.1056/NEJMoa1914347
105. Gauthier J, Hirayama AV, Purushe J, et al. Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. *Blood*. 2020;135(19):1650-1660. doi:10.1182/blood.2019002936
106. Rigter LS, Snaebjornsson P, Rosenberg EH, et al. Double somatic mutations in mismatch repair genes are frequent in colorectal cancer after Hodgkin's lymphoma treatment. *Gut*. 2018;67(3):447-455. doi:10.1136/gutjnl-2016-312608

How to cite this article: Wang H, Zhang W, Yang J, Zhou K. The resistance mechanisms and treatment strategies of BTK inhibitors in B-cell lymphoma. *Hematol Oncol*. 2021;39(5):605-615. https://doi.org/10.1002/hon.2933