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Review Article

Bruton's Tyrosine Kinase (BTK) Mutations in Chronic Lymphocytic Leukemia (CLL): A Clinical View

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Abstract. Bruton's tyrosine kinase inhibitors (BTKis) have reshaped the management of chronic lymphocytic leukemia (CLL). The first-generation BTKi ibrutinib demonstrated significant efficacy, leading to the development of second-generation agents (acalabrutinib, zanubrutinib) with improved selectivity and safety. However, resistance—most often driven by BTK mutations at the cysteine residue at position 481 (C481S)—remains a major therapeutic limitation.
Noncovalent BTKis, such as pirtobrutinib, offer effective options for patients relapsing after covalent BTKi therapy. However, the emergence of novel resistance mutations continues to limit durable responses. As insights into the molecular basis of BTK resistance evolve, routine mutation testing is poised to become integral to personalized treatment in CLL. Future clinical trials are expected to adopt mutation-driven stratification to guide therapeutic sequencing. Ultimately, overcoming BTKi resistance will require innovative strategies, including BTK degraders, bispecific antibodies, and T cell–engaging immunotherapies.

Keywords: CLL; BTK mutations; BTK inhibitors resistance; Noncovalent BTK inhibitors.

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Introduction. Bruton's tyrosine kinase inhibitors (BTKis) have transformed the therapeutic landscape of chronic lymphocytic leukemia (CLL). Ibrutinib, the first-in-class BTKi, demonstrated substantial efficacy in phase III trials, establishing its role in both frontline and relapsed/refractory (R/R) settings.[1-4]

Subsequent to the clinical validation of ibrutinib, second-generation BTKis, including acalabrutinib and zanubrutinib, were developed and evaluated.[5-6] These next-generation agents exhibit advantageous properties, notably improved safety profiles, and, in the case of zanubrutinib, superior efficacy relative to ibrutinib in specific contexts.[7-8] Consequently, these inhibitors have become integral to the therapeutic armamentarium for a substantial proportion of CLL patients requiring continuous pharmacological intervention.[9-10]

Covalent BTKis, including both first- and second-generation agents, exert their therapeutic effect through irreversible binding to the cysteine residue at position 481 (C481) of the BTK protein.[11-12] The development of resistance—most notably via the C481S point mutation—compromises this mechanism by preventing effective drug binding.[12] In addition, activating mutations in Phospholipase C Gamma 2 (PLCG2), a key downstream effector in the B-cell receptor signaling pathway, have been identified as contributors to resistance. These mutations frequently co-occur with BTK mutations, indicating a multifactorial basis for therapeutic failure.[13] Given that second-generation BTKis, such as acalabrutinib and zanubrutinib, rely on

the same C481-binding mechanism, the presence of the C481S mutation similarly compromises their efficacy.[12] These findings underscore the ongoing clinical challenge of overcoming acquired resistance to BTKis in the treatment of CLL.

BTK C481S Mutation in Patients Treated with Covalent BTKi. Long-term investigations have demonstrated that mutations in BTK and PLCG2 occur infrequently among patients with CLL undergoing first-line treatment with covalent BTKis.[14–15] This finding is supported by a large retrospective cohort study presented at the 2024 American Society of Hematology (ASH) meeting, which included 13,940 CLL patients treated with BTKis for more than one year. BTK mutations were identified in only 1.7% of the cohort, primarily among those who received either ibrutinib or acalabrutinib as first-line therapy. Importantly, these mutations were frequently accompanied by TP53 aberrations, observed in 44.5% of cases. However, the study did not establish a definitive correlation between the co-occurrence of these genetic alterations and resistance to BTKi therapy.[15]

Consistent with these findings, a pooled analysis of 238 previously untreated CLL patients from four clinical trials (PCYC-1122e, RESONATE-2, RESONATE-17, and ILLUMINATE) revealed a low incidence of resistance-associated mutations. BTK and PLCG2 mutations were detected in 3% and 2% of patients, respectively, with only 1% harboring both mutations at the last follow-up.[14] Notably, the presence of these mutations was not associated with clinical progression. These data suggest that, in the absence of overt disease progression, the detection of BTK or PLCG2 mutations may not warrant immediate therapeutic intervention or modification.[14]

In contrast, acquired BTK C481S mutations are more frequently observed in patients who develop resistance to BTKis[11,16–23] (**Table 1**). This trend is particularly evident in two recent phase III clinical trials comparing first- and second-generation BTKis in patients with R/R CLL.[17–18]

In the ELEVATE R/R trial, which evaluated acalabrutinib versus ibrutinib in previously treated CLL, emergent BTK mutations at the time of disease progression were identified in 66% of patients receiving acalabrutinib and 37% of those treated with ibrutinib. The median variant allele fraction (VAF) of these mutations was 16.1% and 15.6%, respectively.[17]

Similarly, the ALPINE trial, which compared zanubrutinib with ibrutinib in the R/R CLL setting, assessed paired baseline and progression samples from 52 patients. While no BTK mutations were detected at baseline, 15.3% of patients (zanubrutinib, n = 5; ibrutinib, n = 3) acquired a total of 17 BTK mutations upon progression. Notably, 82.4% of these mutations

Table 1. Prevalence of BTK and non-BTK mutations in studies of BTK inhibitors.

Study	cBTKi	Disease status	Patients with BTK mutations (n)	C481S (%)	C481F (%)	C481R (%)	C481Y (%)	C481G (%)	T474I (%)	L528W (%)	PLCG2 (%)
ERIC[17]	Ibrutinib	R/R	38	92.1%	5.2%	10.5%	18.4%	NA	NA	NA	12%
ELEVATE R/R[18]	Ibrutinib	R/R	11	90.5%	18.2%	3.2%	9.1%		0%	3.3%	6%
FILO[20]	Ibrutinib	R/R	17	82.3%	0%	11.7%	11.7%	11.7%	NA	NA	13%
ALPINE[19]	Ibrutinib	R/R	4	75%	0%	0%	0%	0%	0%	0%	0%
Peter MacCallum Cancer Center[22]	Ibrutinib	R/R	24	100%	NA	NA	NA	NA	NA	4.1%	NA
MD Anderson Cancer Center[23]	Ibrutinib	R/R	16	81.2%	25%	6.2%	31.2%	NA	NA	NA	NA
Ohio State Hematology[16]	Ibrutinib	R/R	40	85%	7.5%	2.5%	NA	NA	NA	NA	7%
PCYC-1122, RESONATE-17, RESONATE, RESONATE2, ILLUMINATE[14]	Ibrutinib	R/R	100*	69%*	0%*	7%*	6%*	0%*	0%*	3%*	12.2%
BRUIN Trial[37]	Mostly ibrutinib	R/R	84	NA	NA	NA	NA	NA	NA	NA	8.1%
Hungarian Ibrutinib Resistance Analysis Initiative[26]	Ibrutinib	R/R	32	100%	NA	NA	NA	NA	NA	NA	NA
ALPINE[19]	Zanubrutinib	R/R	5	60%	20%	20%	20%	0%	0%	20%	7.1%
Peter MacCallum Cancer Center[22]	Zanubrutinib	R/R	13	77%	NA	NA	NA	NA	NA	54%	NA
ELEVATE-R/R[18]	Acalabrutinib	R/R	31	90.5%	6.5%	3.2%	6.5%	0%	29%	0%	20%
BRUIN trial[40]	Pirtobrutinib	R/R Previous BTKi	86	4.6%	0%	4.6%	4.6%	0%	25.5%	16.2%	7%

occurred at the C481 residue (zanubrutinib, n = 4; ibrutinib, n = 3).[18]

These clinical trials highlight differences in the incidence of acquired BTK mutations, which may reflect underlying variations in patient characteristics and follow-up duration.[17–18] The higher mutation rate observed in the ELEVATE R/R cohort—enriched for patients with adverse cytogenetic profiles, including del(17p) and del(11q)—suggests a potential link between genomic instability and an increased likelihood of developing resistance mutations.[17]

A recent systematic review and meta-analysis investigated the prevalence of BTK and PLCG2 mutations in patients with CLL who experienced progressive disease (PD) while receiving covalent BTKi therapy.[24] The analysis included 724 patients, 92.1% of whom had confirmed PD. BTK mutations were identified in 52% of cases (95% confidence interval [CI]: 39–64%), with similar rates observed in patients treated with first-generation (53%) and second-generation (51%) BTKis.

Among 620 patients assessed for PLCG2 mutations, the prevalence was 11% (95% CI: 7–17%). Importantly, the occurrence of PLCG2 mutations was significantly correlated with the degree of TP53 disruption ($r = 0.804$, $P = 0.02$) and the duration of BTKi therapy ($r = 0.851$, $P = 0.001$).[24]

While the emergence of somatic mutations is a well-established mechanism of resistance to BTKi therapy, approximately one-third of patients with clinical resistance do not exhibit detectable mutations in BTK or PLCG2.[24] This finding suggests that resistance may also arise through non-genetic, adaptive mechanisms involving the activation of alternative pro-survival signaling pathways in CLL cells. In particular, the PI3K, NF-κB, and MAPK pathways have been implicated in supporting leukemic cell survival despite BTK inhibition.[25]

Moreover, microenvironmental factors—such as enhanced chemokine and integrin signaling driven by the upregulation of chemokine receptors on CLL cells—may further contribute to BTKi resistance.[25]

Collectively, these findings underscore the critical need for ongoing research into therapeutic strategies that target alternative survival pathways. Such approaches may provide a more effective means of overcoming resistance in CLL patients treated with BTKi.[26]

Managing CLL/SLL After BTKi Resistance. In contemporary clinical practice for patients with CLL/small lymphocytic lymphoma (CLL/SLL), the dual challenges of treatment-related adverse events and, more critically, disease progression frequently necessitate discontinuation of BTKi therapy.[27] Among these, disease progression constitutes a principal concern, with reported incidence rates ranging from 15% to 30%, depending on the line of therapy.[27] Importantly, a longitudinal analysis spanning a decade documented disease progression in 38% of patients receiving ibrutinib as first-line treatment, highlighting the limitations of long-term BTKi monotherapy in a subset of patients.[28]

The emergence of resistance mutations following treatment with covalent BTKis (cBTKis), particularly those affecting the C481S binding site, significantly undermines the efficacy of subsequent cBTKi retreatment. This clinical challenge necessitates a strategic shift toward alternative therapeutic modalities, notably BCL-2 inhibitor (BCL2i)-based regimens and noncovalent BTKis (ncBTKis).[29–34] While BCL2i therapies offer a potential treatment avenue for patients without prior exposure, definitive, high-quality clinical evidence supporting their efficacy in the post-cBTKi setting remains limited and warrants further investigation.

The broad generalizability of the pivotal phase III MURANO trial—which demonstrated superior outcomes for venetoclax plus rituximab in patients with R/R CLL—is constrained in the context of post-cBTKi treatment. This limitation is primarily due to the underrepresentation of patients with prior B-cell receptor inhibitor (BCRi) exposure, who comprised only 3% (n = 5/194) of the study cohort.[29]

Nevertheless, independent studies provide valuable insights into the utility of BCL2i-based strategies following BTKi failure. In a retrospective analysis by Jones et al., venetoclax monotherapy yielded a 65% objective response rate (ORR) and median progression-free survival (PFS) of approximately 25 months in heavily pretreated patients who had progressed on ibrutinib.[31] Similarly, Kater et al. reported a 64% ORR and a median PFS of 23 months among patients with prior BCRi exposure treated with venetoclax monotherapy.[30]

Real-world data further support these findings. The CLL Collaborative Study of Real-World Evidence (CORE) reported that 14% of patients initiating cBTKi therapy subsequently received BCL2i-based regimens, with 8.9% receiving venetoclax monotherapy. The median time to the next treatment (TTNT) in this cohort was approximately 30 months.[32] Consistently, a mono-institutional series from the Mayo Clinic observed a median TTNT or discontinuation (TTNT-D) of 30 months following venetoclax initiation in patients with cBTKi-resistant CLL.[33]

Comparable outcomes have also been observed with the noncovalent BTKi (nc-BTKi) pirtobrutinib. In the BRUIN CLL-321 trial, a phase 1/2 study comparing pirtobrutinib to the investigator's choice in patients previously treated with covalent BTK (cBTKis)—85% of whom discontinued due to disease progression—the median TTNT was 25 months.[34] Furthermore, a recent

matching-adjusted indirect comparison (MAIC) analysis indicated comparable efficacy between pirtobrutinib and continuous venetoclax monotherapy in R/R CLL patients with prior cBTKi exposure.[35]

Although therapeutic strategies involving BCL-2 inhibitor-based regimens and ncBTK inhibitors have demonstrated promising clinical activity, outcomes for patients with CLL who progress following cBTKi therapy remain suboptimal. These findings highlight a significant and ongoing unmet clinical need in the post-cBTKi treatment setting, emphasizing the necessity for continued research into more durable and mechanistically novel therapeutic approaches.

Variant BTK Mutations and Their Role in Resistance to Second-Generation BTKis. In addition to well-characterized BTK and PLCG2 mutations, the emergence of novel mutations has been observed with the increasing use of second-generation BTKis. Within this evolving therapeutic landscape, BTK mutations in CLL can be broadly classified into two functional categories: kinase-proficient mutations—such as T474I/S and C481S—and kinase-impaired mutations, which include M437R, V416L, C481Y/R/F, and L528W.[25,36–37] Notably, despite reduced or absent kinase activity, many kinase-impaired variants retain the ability to propagate downstream signaling.

Among these, the L528W mutation is of particular interest. Preclinical studies have shown that CLL cells harboring this mutation maintain activation of phospholipase C gamma (PLCγ), suggesting that BCR-mediated signaling remains functionally intact even in the context of impaired BTK kinase activity.[25] This observation implies a more complex mechanism of signal transduction in cells expressing the L528W variant, likely involving compensatory or parallel signaling pathways.[25]

Emerging preclinical evidence indicates that kinases such as hematopoietic cell kinase (HCK) and integrin-linked kinase (ILK) may contribute to these alternative pro-survival signaling mechanisms in CLL cells with the L528W mutation.[25,38] These findings highlight the need for further mechanistic studies to elucidate the full spectrum of signaling networks that sustain CLL cell viability in the presence of kinase-impaired BTK variants.

Researchers at the Peter MacCallum Cancer Center were the first to identify the BTK L528W mutation in four patients with CLL who experienced disease progression during zanubrutinib therapy.[39] A subsequent study corroborated these findings, detecting the L528W mutation in 7 (53.8%) of 13 patients with disease progression on zanubrutinib, in contrast to only 1 (4.1%) of 24 patients progressing on ibrutinib.[40] Similarly, in the ALPINE study—which utilized a highly sensitive mutation detection assay—non-C481 mutations were observed in 12.5% (3/24) of zanubrutinib-treated patients (L528W: n = 2; A428D: n = 1), while no such mutations were identified among patients receiving ibrutinib.[18]

In addition to the L528W mutation, the BTK T474I gatekeeper mutation has emerged as a significant resistance mechanism in patients undergoing acalabrutinib treatment. Researchers at Ohio State University reported the initial case associating the T474I mutation with acalabrutinib therapy.[41] Furthermore, a comprehensive analysis from the ELEVATE-RR trial identified the T474I mutation in 29% of patients who experienced disease progression while receiving acalabrutinib.[24]

Preclinical data indicate that the T474I, a kinase-proficient mutation exhibiting enhanced autophosphorylation relative to wild-type BTK, maintains active signaling capacity.[25,42] Moreover, in vitro studies suggest that T474 mutations, especially when co-occurring with the C481S mutation, may synergistically enhance BTK enzymatic activity. However, this combined mutation profile has not yet been validated in clinical specimens.[25,42]

Noncovalent BTKis and the Growing Recognition of Non-C481 Mutations. The advent of nc-BTKis represents a promising therapeutic alternative to traditional irreversible cBTKis.[34,43] In contrast to covalent inhibitors, which irreversibly bind to the C481 residue of BTK, ncBTKis interact reversibly within the ATP-binding pocket, enabling sustained inhibition independent of C481 mutation status.[44] These agents are characterized by distinct pharmacologic profiles, including extended half-lives and favorable binding kinetics, which may enhance their therapeutic potential in patients with resistance to covalent BTKis.[43]

Among the most clinically advanced agents in this class, pirtobrutinib has demonstrated robust efficacy in R/R CLL, including in patients harboring BTK C481 mutations. The phase I/II BRUIN study reported meaningful clinical responses in patients previously treated with cBTKis, underscoring the therapeutic potential of pirtobrutinib in the R/R CLL setting.[34,43]

More recently, results from the BRUIN CLL-321 trial (NCT04666038)—the first randomized phase III study evaluating pirtobrutinib in patients with prior cBTKi exposure—were presented at the 2024 ASH meeting.[45] This trial demonstrated a significant PFS benefit with pirtobrutinib compared to the investigator's choice of therapy (median PFS: 14.0 months vs. 8.7 months, respectively). Notably, clinical benefit was observed across a range of high-risk subgroups, including patients with BTK C481S and PLCG2 mutations.[45]

Comparable efficacy has been observed with other noncovalent BTKis. In the phase I/II BELLWAVE-001 trial, nemtabrutinib achieved an ORR of 56% in patients

with R/R CLL, with a median duration of response (DOR) of 24.4 months and a median PFS of 26.3 months.[46] Notably, 95% of participants had prior covalent BTKi exposure, and BTK^C481S mutations were present in 63% of patients.[47] In contrast, vecabrutinib demonstrated more limited efficacy. A phase Ib dose-escalation study (NCT03037645) enrolled 39 patients with B-cell malignancies—predominantly CLL (77%)—all of whom had received prior BTKi therapy. Among them, 45% harbored BTKC481 mutations, and 18% had PLCG2 mutations. However, the anti-tumor activity observed at studied dose levels was deemed insufficient to warrant phase II expansion, underscoring the variability in clinical activity among noncovalent BTKis.[48]

Finally, fenebrutinib (formerly GDC-0853), a reversible ncBTKi, has been evaluated in a phase 1 trial (NCT01991184) involving 24 patients, 25% of whom carried BTK^C481S mutations. The trial reported an ORR of 33%, with a higher response rate of 50% among patients with CLL (n = 7).[49] Although development for B-cell malignancies has been discontinued, fenebrutinib is currently being studied in other indications, such as multiple sclerosis (NCT04544449).

It is noteworthy that a subset of patients exhibited acquired resistance to pirtobrutinib. Recent investigations have elucidated mechanisms of resistance, including the emergence of novel *BTK* mutations occurring outside the canonical C481 binding domain.[36,42] A post-hoc analysis of the BRUIN CLL-321 cohort revealed that a substantial proportion of patients (68%) developed acquired mutations upon disease progression, with *BTK* mutations identified in 44% and *PLCγ2* mutations in 24%. Within the cohort of patients with acquired *BTK* mutations, the *T474* and *L528W* substitutions were prevalent.[50] Given the established association of these mutations with resistance to second-generation BTK inhibitors acalabrutinib and zanubrutinib, their emergence may confer cross-resistance to this class of agents as well as to pirtobrutinib.[36,42] Interestingly, several of these resistance-associated *BTK* mutations (e.g., *V416L*, *A428D*, *M437R*, *L528W*) demonstrated reduced kinase activity yet paradoxically sustained BCR signaling and AKT pathway activation, suggesting a kinase-independent scaffolding role for BTK in these contexts.[25]

Conclusions. The heterogeneity of mutation profiles observed across various BTK inhibitors underscores the significance of their distinct molecular specificities, which consequently give rise to unique resistance patterns and differential treatment efficacies.[42] Of note, the pathophysiology of BTKi resistance in the context of emergent *BTK* mutations has been the subject of recent detailed analysis.[51] Observations indicate that *BTK* C481S-mutant clones frequently coexist with and do not achieve complete competitive exclusion of *BTK* wild-type (WT) clones at relapse, and that suggests a model of resistance evolution predicated on clonal cooperation rather than strictly linear clonal selection. Single-cell transcriptomic analyses have demonstrated distinct phenotypic states between WT and mutant CLL cells, with potential interactions mediated via paracrine signaling pathways, including interferon- and IL4/CLLU1-mediated mechanisms. These findings challenge the conventional mutation-centric paradigm of resistance and underscore the significance of intratumoral heterogeneity and microenvironmental influences. This heterogeneity could potentially support the rationale for combinatorial therapeutic strategies aimed at targeting both *BTK*-mutant and WT subpopulations, as well as the signaling networks that facilitate their cooperative survival under BTKi selective pressure.[51]

Notably, the field of *BTK* mutation research is progressing towards a model wherein resistance profiling may assume a pivotal role in guiding therapeutic decision-making, thereby enabling a more personalized and targeted approach to CLL management.[52] Data concerning the binding moieties of BTK inhibitors have revealed that non-C481 BTK mutants, specifically V416L, A428D, M437R, T474I, and L528W, not only confer resistance to the noncovalent inhibitor pirtobrutinib but also extend this resistance to both covalent (ibrutinib) and other noncovalent BTK inhibitors (nemtabrutinib, vecahrutinib, and fenebrutinib).[53-54] Mechanistically, these resistance-conferring mutations (V416L, A428D, M437R, and L528W) have been associated with decreased BTK kinase activity, as evidenced by the absence of BTK Y223 phosphorylation.[25,54] Intriguingly, despite this diminished BTK activation, downstream signaling pathways involving AKT and ERK, alongside hyperactivated calcium release, were sustained even in the presence of BTK inhibition.[54]

The unresolved question of whether pirtobrutinib should be integrated into earlier lines of therapy, including frontline treatment or prior to the administration of cBTKi, is currently being addressed by an ongoing clinical trial (NCT05254743) comparing pirtobrutinib with ibrutinib in previously untreated patients with CLL. The anticipated data from this trial will be crucial in determining the efficacy and safety profile of pirtobrutinib in the frontline setting. Nevertheless, it is noteworthy that all patients exhibiting BTK L528W or T474I mutations following pirtobrutinib resistance had prior exposure to ibrutinib, leaving it uncertain whether similar mutations would arise in patients receiving pirtobrutinib as their initial BTKi therapy.[50,54] Of note, nemtabrutinib, the second noncovalent BTK inhibitor (ncBTKi) most extensively studied in clinical trials after pirtobrutinib, is not anticipated to exhibit efficacy

Table 2. Preclinical data on the binding affinity of available BTK inhibitors to both wild-type and mutant BTK in CLL cells.

Inhibitor Type	Drug	Wild Type	C481S *(Proficient Mutation)*	T474I *(Proficient Mutation)*	L528W *(Dead Mutation)*
Covalent BTK Inhibitors	Ibrutinib	Normal activ.	Decreased activity	Normal activity	No binding detected
	Acalabrutinib	Normal activ.	Decreased activity	Decreased activity	Decreased activity
	Zanubrutinib	Normal activ.	Decreased activity	Decreased activity	No binding detected
Noncovalent BTK Inhibitor	Pirtobrutinib	Normal activ.	Normal activity	Decreased activity	No binding detected

Legend: Green = Normal kinase activity or binding, Yellow = Reduced kinase activity or binding, Red = No detectable binding.

against either the T474I or L528W mutations.[54]

From a clinical perspective, given the elevated probability of detecting BTK mutations in patients refractory to BTKis, mutational status warrants meticulous evaluation as a standard in clinical practice.[52] Consequently, therapeutic decision-making for patients exhibiting BTK inhibitor resistance should be guided by their specific mutational profile, thereby enabling the selection of treatment options that are unlikely to be affected by the same resistance mechanisms (**Table 2**).

Adoption of fixed-duration therapeutic protocols is a significant strategy to impede the emergence of acquired BTK mutations.[55] The CAPTIVATE study demonstrated that a fixed-duration combination of ibrutinib and venetoclax mitigates the selective pressures associated with continuous BTK inhibition, consequently averting the emergence of detectable BTK mutations upon relapse in CLL.[56] Current clinical investigations assessing various combinations of acalabrutinib, zanubrutinib, and pirtobrutinib may further optimize future treatment paradigms.[57-59]

Considering the complexity of BTK inhibitor resistance mechanisms, the advancement of next-generation BTK inhibitor therapy remains a critical area of research. Key findings from the 2024 American Society of Hematology (ASH) meeting, particularly from the CadAnCe-101 and NX-5948-301 trials, underscore the potential of these novel agents in treating heavily pretreated CLL/SLL patients who have developed resistance to conventional BTK inhibitors.[60-61] These trials suggest that targeting the BTK pathway through innovative mechanisms, such as E3 ligase-mediated degradation, may provide a viable therapeutic alternative for high-risk, relapsed/refractory CLL patients. The emerging safety and efficacy data from these trials indicate that these novel agents may play a pivotal role in the evolution of treatment regimens for CLL/SLL. Although protein degraders were initially believed to circumvent resistance associated with BTK mutations, recent evidence suggests that a mutation within the BTK kinase domain can compromise the activity of a BTK degrader under clinical evaluation. Notably, patients with CLL cells harboring the A428D BTK mutation may exhibit diminished sensitivity to treatment with BGB-16673 or NX-2127.[62]

Another active area of investigation includes the potential use of T-cell-engaging therapies in heavily treated CLL patients with associated BTK mutations. Clinical investigations have demonstrated the capacity of chimeric antigen receptor (CAR) T-cells to elicit sustained remissions, exhibiting favorable overall response rates in such patients.[63-64] Furthermore, bispecific antibodies are under investigation as immunotherapeutic approaches, revealing encouraging preclinical and preliminary clinical findings in the effective targeting of CLL cells.[65-66] A significant impediment in the application of T-cell-based therapies for CLL is the acquired T-cell impairment observed in affected individuals.[67] To address these limitations, current research is exploring strategies such as the integration of targeted pharmacological agents with cellular immunotherapies, the modification of CAR constructs, and the incorporation of immunomodulatory compounds within the manufacturing protocol.[68]

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