# Second-Generation Brutons Tyrosine Kinase Inhibitors

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## Abstract

Bruton tyrosine kinase (BTK) has been implicated in the pathogenesis of chronic lymphocytic leukemia (CLL) and other B-cell lymphoproliferative disorders. The first-generation BTK inhibitor, ibrutinib, has shown remarkable clinical activity in CLL, mantle cell lymphoma, marginal zone lymphoma, and Waldenström macroglobulinemia, both as monotherapy and as part of combination therapy. Despite the high response rates, subsequent resistance as well as adverse effects remain challenges. Numerous second-generation BTK inhibitors are in clinical trials at varying stages of development. In this review, we discuss 3 of these compounds: acalabrutinib (ACP-196), BGB-3111, and ONO/GS-4059.

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## Introduction

First described in the 1950s, the syndrome Bruton X-linked agammaglobulinemia was identified as a humoral immunodeficiency. The Bruton tyrosine kinase (BTK) gene, *BTK*, was cloned in 1993. It consists of 19 exons, and more than 250 mutations have been described in the BTKBase database to date. The *BTK* gene is on the q arm of the X chromosome at the g21.1-22 locus, and the BTK protein is the transcription product. BTK is a member of the TEC family of tyrosine kinases and is found in the cytoplasm. The protein is normally phosphorylated after the B-cell receptor is activated, and it is involved in the signaling pathway that leads to B-cell differentiation (**Figure**). A deficiency of a functional protein leads to an arrest in B-cell maturation.[1-5]

After the gene was cloned, numerous studies further defined its role in B-cell receptor (BCR) signaling and maturation. It promotes cell cycle progression and blunts apoptosis via the Nf-κB and BCL-Xl pathways, respectively. The dependence of mature B cells on BTK signaling was shown in mouse models. In vitro studies revealed not only the necessity of the BCR for cell survival, but a viable small molecule target. This led to the first published report of the irreversible BCR inhibitor, ibrutinib, which selectively blocked B-cell receptor signaling and induced clinical responses in canine non-Hodgkin lymphoma (NHL) models. This was later followed by studies in human-derived chronic lymphocytic leukemia (CLL) cell lines, proving its attractiveness as a therapeutic target for B-cell malignancies.[6-12]

## Efficacy

In 2012, the clinical efficacy of ibrutinib was first reported in a phase I trial consisting of 50 patients with relapsed/refractory (r/r) B-cell malignancies; the objective response rate (ORR) was 60% (69% for CLL and for small lymphocytic leukemia [SLL]). A subsequent phase I/II trial in CLL/SLL resulted in an ORR of 71%. The superiority of ibrutinib over ofatumumab in the r/r setting was demonstrated in the RESONATE study, showing a 90% versus 81% overall survival at 12 months. The response rate was also significantly higher with ibrutinib, with an ORR of 42.6% versus 4.1%.[13-15]

Several combination studies have been published. A combination study of ibrutinib and ofatumumab in CLL, SLL, and prolymphocytic leukemia in 3 dosing cohorts showed response rates of 100%, 79%, and 71% for the ibrutinib lead-in, combination lead-in, and ofatumumab lead-in cohorts, respectively. A study of ibrutinib with rituximab in high-risk patients provided an ORR of 95%. A randomized trial comparing bendamustine/rituximab plus or minus ibrutinib showed improvements in median progression-free survival (PFS) (13.3 months vs not reached) and ORR (82.7% vs 67.8%).[16-18]

In the treatment-naïve population, the randomized phase III trial of ibrutinib versus chlorambucil showed a 13% improvement in 24-month survival and 51% improvement in ORR. Ibrutinib has efficacy in the high-risk *TP53* mutated/17p deleted population as well. A phase II study indicated 97% and 80% ORRs in treatment-naïve and r/r patients, respectively. In the largest trial ever reporting outcomes in r/r patients with CLL and 17p deletion, 134 patients treated with ibrutinib had an 83% ORR and a 24-month PFS of 63%. The tolerability of ibrutinib as frontline therapy for CLL in an older population was also studied, revealing a very manageable adverse event (AE) profile.[19-22]

The data in other B-cell malignancies are also impressive. In relapsed mantle cell lymphoma (MCL), the first phase II trial with ibrutinib provided an ORR of 68%; in combination with

**TABLE. Summaries of Highlighted Trials Related to BTK Inhibitors (other than ibrutinib)**

| Compound | Phase of Trial | N | Tumor Subtypes | Line | Overall Response Rate | Grade 3/4 Toxicities |
|---|---|---|---|---|---|---|
| ONO/GS-4059 | I | 90 | CLL/SLL, MCL, DLBCL, FL, MZL, and WM | r/r | CLL: 96% (n = 24/25); MCL: 92% (n = 11/12); DLBCL: 35% (n = 11/31) | n = 42 |
| BGB-3111 | I | 25 | CLL/SLL, MCL, DLBCL, HCL, FL, MZL, and WM | r/r | Entire group: 88% (n = 22/25) | n = 21 |
| Acalabrutinib | I/II | 61 | CLL/SLL | r/r | 95% (n = 53/61) | n = 11 |

CLL indicates chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; r/r, relapsed/refractory; SLL, small lymphocytic leukemia; WM, Waldenström macroglobulinemia.

rituximab, the ORR was 88%. In another randomized trial in r/r MCL with temsirolimus as the comparator arm, the PFS improved by 8 months—14.6 versus 6.2 months— and the ORR improved from 40% to 72%.[23,24]

In r/r Waldenström macroglobulinemia (WM), ibrutinib also has activity. The expanded phase II study for r/r WM showed an ORR of 90.5%. Patients with the mutation $MYD88$ L265P and $CXCR$ WT had an ORR of 100%. Patients with the mutations $MYD88$ L265P and $CXCR4$ WHIM (indicating warts, hypogammaglobulinemia, infections, and myelokathexis) had an ORR of 85.7%, and those with $MYD88$ WT $CXCR4$ WHIM had an ORR of 71.4%. It has also shown early promise in r/r diffuse large B-cell lymphoma (DLBCL). When combined with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), the ORR was 100% in the activated B-cell (ABC) subtype. As a single agent, the ORR in the ABC subtype of r/r DLBCL was 25%.[25-27]

## Resistance
### Chronic Lymphocytic Leukemia
Primary and secondary resistance to therapy remains a clinical challenge. Whole genome sequencing performed in 5 of 6 longitudinally-followed patients with CLL who developed ibrutinib resistance showed a C481S substitution in $BTK$. In another analysis, 10 of 10 patients with CLL and Richter transformation had either a $BTK$ C481S mutation or a $PLCG2$ mutation. The presence of the $BTK$ C481S mutation leads to loss of irreversible binding. The C481S mutation has 25-fold less sensitivity to ibrutinib than does the wild type.

Mutated BTK activation causes downstream gene expression, cell signaling, and cell behavior changes promoting cell survival. These mutations retain sustained sensitivity to numerous agents, including dasatinib, idelalisib, and SYK inhibitors.[28-32]

### Mantle Cell Lymphoma
Primary resistance in MCL appears to be more complicated. Whole exome/transcriptome profiling of serial biopsies, from ibrutinib initiation until drug resistance, in a patient with MCL showed the evolution of the $BTK$ C481S mutation. Data revealed amplified activation of the $BTK$, $AKT$, and CXCR4-CXCL12 pathways, thought to be mediators of secondary resistance. Other experiments have shown that in ibrutinib-resistant MCL cell lines, cell proliferation is mediated through a nonclassical NF-κB pathway, via $TRAF2$ and $TRAF3$ mutations.[33,34]

### Diffuse Large B-cell Lymphoma
DLBCL comprises a genetically heterogeneous group of B-cell lymphomas. The activated B cell–like (ABC) subtype has a gain-of-function $CD79A/B$ ITAM motif mutation. $MYD88$ L265P mutations are also seen more commonly in the ABC than the germinal center subtype. The response rates to ibrutinib for ABC and germinal center B cell–like (GCB) tumors were 38% and 5%, respectively. Tumors with a mutation in $MYD88$ or $CD79A/B$ WT were noted to be more sensitive to ibrutinib than tumors without such mutations.[35-37]
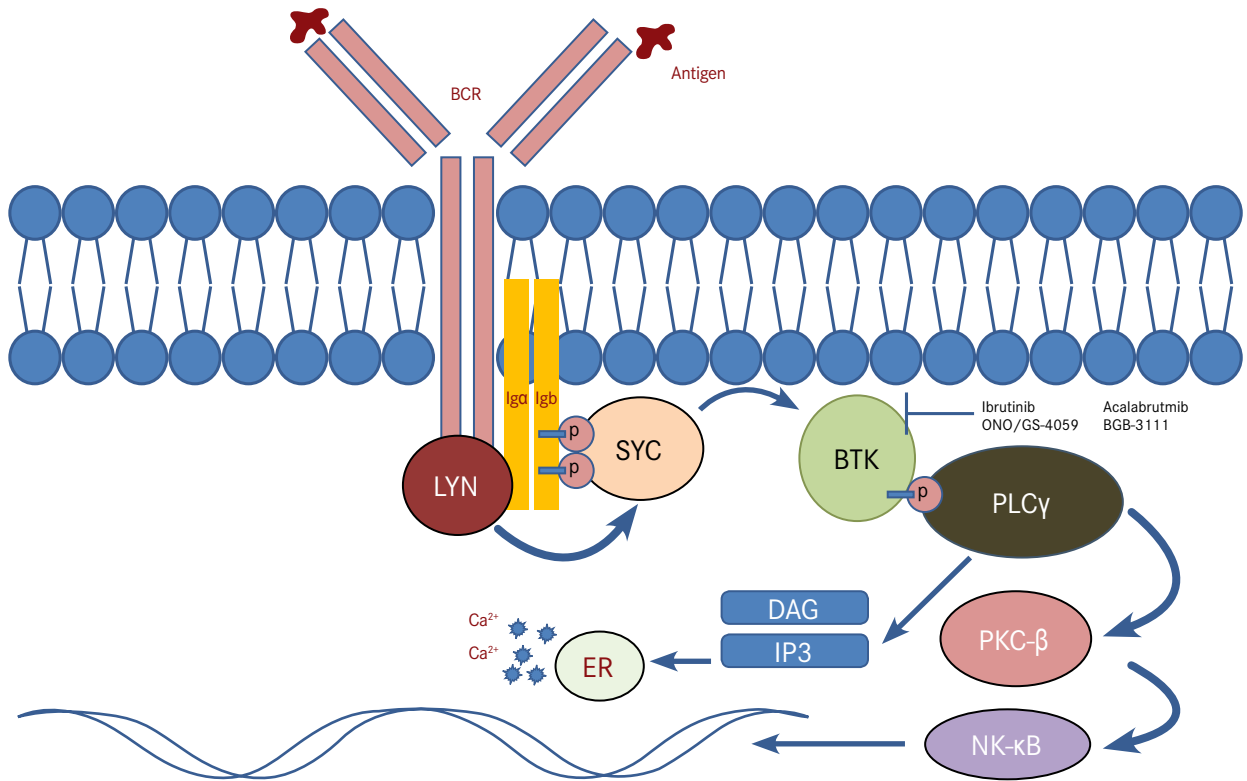
### Waldenstrom Macroglobulinemia
In the phase II study of ibrutinib in r/r WM, the patients with the mutations $MYD88$ L265P and $CXCR4$ WHIM had an ORR of 85.7%, and those with $MYD88$ WT $CXCR4$ WHIM had a lower ORR of 71.4%. It is thought the WHIM-like $CXCR4$ S338X mutation ($CXCR4$ WHIM) allows for a bypass circuit to the mTOR-AKT pathway in the setting of the $MYD88$ L265P mutation, thus conferring resistance to ibrutinib.[38,39]

### Other BTK Inhibitors
Highlighted trials related to BTK inhibitors, other than ibrutinib, are highlighted in the **Table**.

### Acalabrutinib
Acalabrutinib (ACP-196) is a second-generation BTK inhibitor that irreversibly binds the BTK cysteine domain. It has higher selectivity for BTK as compared with other kinases, including MEC, PDGFR, EGFR, ITK, and others. The selectivity is thought to be due to acalabrutinib's propiolamide side group versus ibrutinib's acrylamide side group. The propiolamide

**FIGURE. BTK Signaling Pathway in the B Lymphocyte**



Activation of Bruton tyrosine kinase (BTK) by the antigen-bound activated B-cell receptor leads to phosphorylation of BTK. This in turn promotes both cell survival and antiapoptotic mechanisms. Inhibition of this protein then causes modulation of this signaling pathway, leading to clinical responses seen in several B-cell malignancies.

side group may allow fewer off-target interactions with other kinases such as ITK, EGFR, ERBB2/4, JAK3, LYN, and SRK. While the half maximal inhibitory concentration ($IC_{50}$) for *BTK* is roughly 3 times that of ibrutinib, the $IC_{50}$ against other kinases is much higher.[40-42]

In a phase I/II report of 61 patients with r/r CLL, the ORR at a median follow-up of 14.3 months was 95%, with 53 of 61 patients still on therapy. The phase I portion used 100 mg, 175 mg, 250 mg, and 400 mg once-daily dosing, while the phase II portion used 100 mg twice-daily dosing. The response rate in the 17p-deleted patient cohort was 100%. The response rate in those who had received idelalisib was 100%. Grade 3/4 AEs included diarrhea (n = 1; 2%), weight gain (n = 1; 2%), arthralgia (n = 1; 2%), pyrexia (n = 2; 3%), fatigue (n = 2; 3%), and hypertension (n = 4; 7%). No Richter transformation occurred and only 1 patient progressed.[43]

### ONO/GS-4059

ONO/GS-4059 is a covalent inhibitor with a greater selec-

tivity for BTK than for *LCK*, *FYN*, *LYNA*, and *ITK*. In vitro studies showed that the 50% inhibitory concentration of BTK by ONO/GS-4059 was only 2 nmol/L. ONO/GS-4059 showed promising preclinical efficacy, and this prompted the development of a phase I study in r/r B-cell malignancies.[44-46]

In a phase I study of ONO/GS-4059, 90 patients with a variety of B-cell malignancies, including CLL/SLL, MCL, DLBCL, follicular lymphoma (FL), marginal zone lymphoma (MZL), and WM, were enrolled in a 3+3 dose-escalation study. Doses ranged from 20 mg to 600 mg daily. There were 2 parallel dose-escalation groups, 1 for NHL and 1 for CLL. The overall estimated mean PFS rates in CLL, MCL, and DLBCL were 874, 341, and 54 days, respectively. There was a 96% ORR in patients with CLL (24/25 patients). After 29 months, 34 of 90 patients remained on study, including 21 patients with CLL as well as 13 patients with NHL. Of the patients with CLL, 13 had loss of *TP53* and 21 had unmutated IGHV gene segments. All 12 patients with *TP53*/17p deletion or *TP53* mutations had a response, with 9 remaining on study. In the MCL

group, 11 of 12 evaluable patients showed a response (n = 6, partial response [PR]; and n = 5, complete response/unconfirmed complete response [CR/CRu]). Eight of 12 patients remained on study. In the DLBCL cohort (31/35 ABC), 11 of 31 (35%) showed a response (9 PRs and 2 CR/CRus).[47]

A total of 171 AEs were reported, 75% of which were grade 1/2. Grade 3/4 toxicities included neutropenia (n = 9; 10%), anemia (n = 12; 13.3%), and thrombocytopenia (n = 12; 13.3%). Ten patients discontinued therapy because of AEs/dose-limiting toxicities (DLTs) (n = 5 [CLL] and n = 5 [other NHL]). There was 1 reported case of new-onset atrial fibrillation, which was not thought to be drug related. There were no grade 3/4 cases of diarrhea or arthralgia. In the CLL dose-expansion cohort, the maximum tolerated dose (MTD) of 600 mg daily was reached without DLTs. In the lymphoma cohort, an MTD of 480 mg once daily was reached because 4 patients experienced DLTs (n = 1 each, for urticarial reaction, maculopapular cutaneous rash, nonimmune drug reaction, and cutaneous rash). It is unclear why the DLTs were seen in NHL versus CLL. Other grade 3/4 toxicities included 5 lower respiratory tract infections as well as 1 urticarial rash.

### BGB-3111

BGB-3111 is an irreversible inhibitor of BTK. In preclinical models of MCL and DLBCL, it inhibited BTK auto-phosphorylation and cell proliferation. Cell culture and biochemical assays with BGB-3111 showed less off-target kinase inhibition than was seen with ibrutinib. The $IC_{50}$ ratio of BGB-3111 to ibrutinib for non-BTK kinases (TEK, EGFR, ITK, JAK3, and HER2) ranged from 2- to 70-fold. The $IC_{50}$ ratio:ratio BGB-3111:ibrutinib for BTK was 0.5. BGB-3111 was nearly 10 times weaker at inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity. It has 3-fold higher potency compared with ibrutinib; it also demonstrated dose-dependent antitumor effects against REC-1 MCL xenografts, and prolongation of overall survival in a xenograft model.[48]

In the phase I trial, 25 patients with various B-cell malignancies were enrolled. Diagnoses included CLL (n = 8), MCL (n = 6), WM (n = 6), DLBCL (n = 2), FL (n = 1), MZL (n = 1), and HCL (n = 1). Patients were treated in 5 dosing cohorts: 40, 80, 160, or 320 mg once daily, or 160 mg twice daily. Pharmacokinetic studies showed a sustained 24-hour BTK occupancy in peripheral blood mononuclear cells as well as in lymph nodes for all patients at all doses. Twenty-two of 25 patients had a response, with 15 PRs, 1 CR, and 6 stable disease. There were 21 grade 3/4 AEs, 3 of which were believed to be drug-related. There were no cases of atrial fibrillation/flutter.[49]

### Conclusions

The BTK pathway plays a crucial role in the pathogenesis of B-cell malignancies. Targeting BTK has changed the treatment landscape for B-cell malignancies. Although BTK inhibition has found a role in CLL, WM, MZL, and MCL, its application to other B-cell malignancies is under evaluation.

Better understanding of the structural characteristics of ibrutinib has allowed for the development of other potent, selective inhibitors. As the data on long-term efficacy and safety of ibrutinib mature, resistance and AEs remain as clinical challenges. Further elucidating resistance mechanisms will guide the development of the next generation of BTK inhibitors. Randomized trial data are needed to better address their true efficacy and AE profile. Lastly, their role as monotherapy and in combination therapy will help fine-tune the treatment armamentarium for B-cell malignancies.

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