

Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology

August 2013

The Importance of the BTK Pathway in B-Cell Malignancies

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Abstract: Bruton's tyrosine kinase (BTK) is an intermediate signaling molecule in the B-cell receptor signaling pathway that mediates the survival and expansion of both normal and malignant B cells. Within the last several years, BTK has become the focus of targeted therapies designed to disrupt the activity of the B-cell receptor signal transduction pathway in various B-cell malignancies. Ibrutinib, a small molecule that interferes with BTK tyrosine kinase activity, has been shown to disrupt B-cell survival in vitro and has demonstrated efficacy in phase I and II clinical trials, with particularly encouraging responses and duration of response reported in patients with chronic lymphocytic leukemia (CLL) and mantle cell lymphoma. CLL patients treated with a BTK inhibitor typically show a pattern of clinical response that includes a rapid reduction in lymphadenopathy accompanied by transient lymphocytosis, likely reflecting a redistribution of tumor cells between different anatomic compartments. In this monograph, 3 experts discuss the importance of the BTK pathway in aggressive and indolent B-cell malignancies, safety and efficacy findings from recent clinical trials of BTK inhibitors, and how treatment of B-cell malignancies is likely to change in the near future with the addition of BTK inhibitors.

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Function of the BTK Pathway in B-Cell Malignancies

Jan A. Burger, MD, PhD

Bruton's tyrosine kinase (BTK) is an intermediate signaling molecule that is most well known for its role in the B-cell receptor signaling pathway. It transmits signals from the cell surface to the cytoplasm and into the nucleus. Activation of this pathway ultimately results in the survival and expansion of both normal and malignant B cells. In normal B cells, the function of the pathway is to select antigen-specific B cells. In lymphatic tissues, after these cells are selected by the antigen, they expand in concert with other signals from the microenvironment, which includes T cells and other cells.

It has recently been recognized that B-cell receptor signaling plays a role in various B-cell malignancies, and therefore inhibition of this signaling pathway could be beneficial for the treatment of these cancers.¹ It is thought that the function of the B-cell receptor signaling pathway in B-cell malignancies is similar to its activity in normal B cells, and that it helps the neoplastic B cells in lymphoma patients and B-cell leukemia patients to survive and expand. This hypothesis is based mostly on indirect evidence. For example, gene expression profiling has shown that molecules in the B-cell receptor signaling

Table 1. Selected Ongoing Clinical Trials of Ibrutinib in B-Cell Malignancies

Study	Study Phase	Primary Objectives	Secondary Objectives	Estimated Enrollment	Clinical Trials.gov Identifier	Status
Ibrutinib Versus Ofatumumab in Relapsed or Refractory CLL (RESONATE) ¹²	III	PFS	OS, ORR, hematological improvements	350	NCT01578707	Recruiting, estimated completion in 07/2015
PCI-32765 Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naïve CLL or SLL (RESONATE-2) ¹³	III	PFS	ORR, MRD negative CR, safety	272	NCT01722487	Enrollment started 01/2013, estimated completion in 02/2016
PCI-32765 (Ibrutinib) in Treating Patients With Relapsed or Refractory CLL, SLL, or B-Cell PLL ¹⁴	II	2-year PFS	ORR, duration of response, OS	75	NCT01589302	Recruiting, estimated completion in 12/2014
Multicenter Phase II Study of PCI-32765 (Ibrutinib) in Patients With Relapsed or Refractory CLL or SLL With 17p Deletion (RESONATE-17) ¹⁵	II	ORR	Duration of response, PFS, OS, safety	111	NCT01744691	Recruiting, estimated completion in 03/2016
Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory CLL or SLL (HELIOS) ¹⁶	II	PFS	ORR, OS, side effects	580	NCT01611090	Recruiting, estimated completion in 08/2015
Safety and Tolerability Study of PCI-32765 Combined With FCR and Bendamustine in CLL ¹⁷	I/II	Prolonged hematologic toxicity	Adverse events, ORR	60	NCT01292135	No longer recruiting, estimated completion in 03/2013

CLL=chronic lymphocytic leukemia; CR=complete response; FCR=fludarabine/cyclophosphamide/rituximab; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PLL=prolymphocytic leukemia; PFS=progression-free survival; SLL=small lymphocytic lymphoma.

pathway are activated in areas where chronic lymphocytic leukemia (CLL) cells are growing, which—similar to normal B-cell biology—is mostly in lymphatic tissues.² In addition, this pathway seems to be critical for the survival of certain selected B-cell lymphomas.³

BTK as a Therapeutic Target

The importance of BTK in the B-cell receptor signaling pathway has been established by direct evidence in humans and in mouse models.¹ In humans, mutations in the kinase domain of BTK result in a primary immunodeficiency known as X-linked agammaglobulinemia (XLA), a disease that occurs only in young boys because the gene coding for the BTK protein is located on the X chromosome.⁴ The pediatrician Ogden Bruton reported the first case in the 1950s. Approximately 40 years later, the enzyme BTK was characterized and discovered on the X chromosome. This history further supports the idea that BTK plays a critical role in the function and survival of B cells. Because the blood of XLA patients has no peripheral B cells or immunoglobulins (Ig), these children develop opportunistic infections. Mice with a mutation in this gene have a severe immune defect that mostly affects the B-cell compartment.⁵

With this background, it has become clear that BTK plays a major role in B-cell function. BTK is a major intermediary in B-cell receptor signaling, and it has been recognized within the last decade as a therapeutic target. Companies have become interested in targeting this enzyme. The lead compound, ibrutinib, is in phase III clinical trials in patients with CLL, mantle cell lymphoma (MCL), and Waldenström's macroglobulinemia (Table 1, Figure 1).⁶

BTK in Malignancies

BTK appears to play a major role in several B-cell malignancies (Table 2). The strongest signal in terms of activity is in CLL, an indolent B-cell malignancy that affects the lymph nodes, the bone marrow, and the blood. However, the cells in this disease divide and are activated in the lymphatic tissues, where they receive signals that activate the B-cell receptor. There may also be autoactivation of the B-cell receptor in these areas. Phase I and II studies of BTK inhibition in CLL patients show a high response rate of approximately 70–80%.^{7,8}

The clinical response to BTK inhibition is characterized by initial lymphocytosis in which the CLL cells are redistributed from the lymphatic tissues into the bloodstream, resulting in rapid shrinkage of lymph nodes. The shrinkage is very dramatic in patients with bulky lymph nodes, which typically resolve within only a few weeks. Other sites of disease infiltration, like the spleen, also resolve very quickly. Basically, the cells are flushed out of these tissues into the peripheral

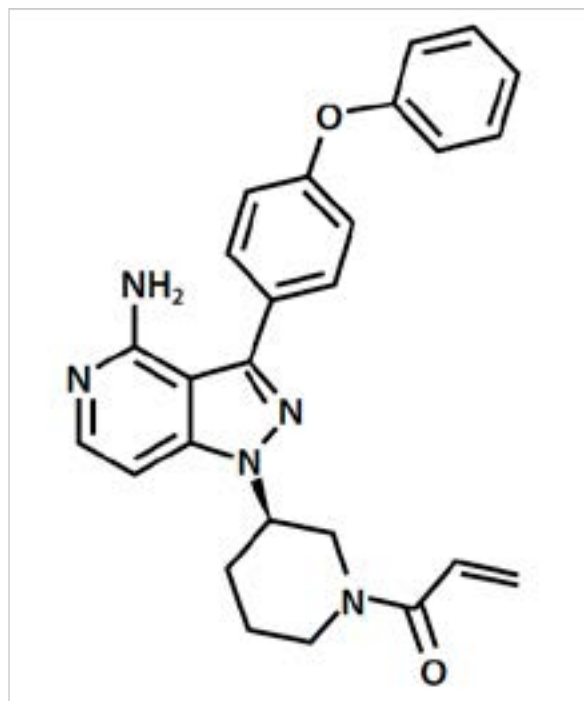


Figure 1. Ibrutinib (PCI-32765) is a selective, oral inhibitor to Bruton's tyrosine kinase.

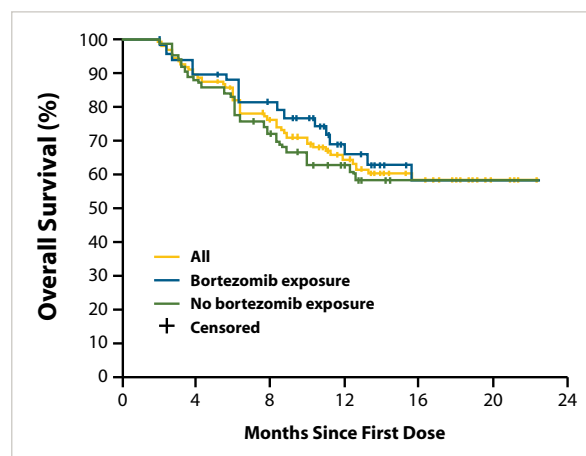


Figure 2. In a phase II trial in patients with relapsed or refractory mantle cell lymphoma, ibrutinib was associated with an estimated overall survival of 58% at 18 months. Adapted from Wang ML et al. *N Engl J Med*. doi:10.1056/NEJMoa1306220.¹¹

bloodstream. In the peripheral blood, they are deprived of the survival and proliferation signals coming from the B-cell receptor and other molecules. Over time, typically several months, these cells are starved and eventually die, at which point objective remissions can be achieved with single-agent treatment with the BTK inhibitor ibrutinib.

This pattern of lymphocytosis followed by remission is probably the most typical characteristic of the response in

Table 2. Expression and Function of BCR-Associated Kinases That Currently Are Targeted in Clinical Trials

Kinase	Structure	Gene Deletion/Mutation	Activating Receptors in B Cells	Function in CLL	Inhibitor(s)
BTK	Nonreceptor tyrosine kinase, member of the Tec family of kinases	In humans: X-linked agammaglobulinemia (XLA, Bruton's agammaglobulinemia), normal pre-B cells in the marrow that fail to mature and enter the blood; in mice: X-linked immunodeficiency (xid)	BCR, integrins, chemokine receptors	CLL cell survival, proliferation, and migration, BCR signaling, chemokine secretion (CCL3, CCL4)	Ibrutinib (PCI-32765), Avila compounds (AVL-292)
PI3 Kinases δ and γ	Class IA PI3K, activity controlled by associated p85 α , p85 β , p55 α , or p50 α subunits	In mice: lack of B1 cells and marginal zone B cells, and deficient antibody responses	BCR, integrins, chemokine receptors	CLL cell survival and migration, chemokine secretion (CCL3, CCL4)	Idelalisib (GS-1101), Infinity compounds (IPI-145)

BCR=B-cell receptor; BTK=Bruton's tyrosine kinase; CLL=chronic lymphocytic leukemia.

CLL. It indicates that the B-cell receptor activation pathway plays a major role in CLL and other diseases that respond to ibrutinib and other BTK inhibitors. It also suggests additional effects of BTK that appear to occur outside of the B-cell receptor signaling pathway. This activity has caught the interest of translational researchers because the lymphocyte redistribution—the rapid lymph node shrinkage and the egress of lymphocytes from the tissues into the blood—is not explained by inhibition of B-cell receptor signaling. As a result, there have been subsequent preclinical studies to find an explanation. It was recognized less than 10 years ago that in normal B cells, BTK plays a role in the signaling of other molecules, not just those in the B-cell receptor signaling pathway. In fact, there are receptors and molecules that cause cells to home to the lymphatic tissues.⁹ These signals basically tell the cells to stay there and grow. Two types of molecules are involved: chemokine receptors and adhesion molecules (also known as *homing receptors*). These homing receptors mediate normal B cells, as well as leukemia and lymphoma cells, to attach to lymphatic tissues in the bone marrow and remain there. Once these receptors are disabled—by using a BTK inhibitor or a chemokine receptor inhibitor, for example—then the cells move out of the tissues and into the blood. They also cannot home back into the lymphatic tissues. When BTK is inhibited by using ibrutinib or another related agent, these cells respond much less to homing signals.

It is apparent, therefore, that BTK inhibitors have a dual effect. They affect B-cell receptor signaling, and ultimately block the proliferation and survival of B cells. In addition, these inhibitors interfere with the homing mechanism, which explains why the cells are flushed out of the tissues and enter into the blood. The egress makes room for normal hematopoietic cells. This activity explains the clinical char-

acteristics associated with BTK inhibitors and has allowed a better understanding of how these molecules work.

Another important indicator of how actively these molecules interfere with homing was provided by a recent phase I study by Advani and colleagues.⁷ Patients received ibrutinib for 4 weeks, and then they had a break in the medication for 1 week. Remarkably, lymphocytosis was transient; during the week without ibrutinib, there was a major decrease in the lymphocyte counts because the cells were going back into the tissues. As soon as the patients started taking the drug again, the lymphocytosis increased, causing a saw-tooth pattern in lymphocyte counts. Over time, the sites of infiltration became smaller, until patients achieved remission. The results of this study clearly underscore the point that these kinase inhibitors have a very substantial effect on the migration pattern and homing of these cells.

Similar data are beginning to emerge in MCL. BTK inhibitors act on proliferation as well as the homing mechanism. Cells are being mobilized and exiting the tissues in patients who are on treatment. At the 2012 ASH meeting, Wang and coworkers presented an interim analysis from a phase II study of ibrutinib in relapsed/refractory MCL.¹⁰ The analysis showed that responses to ibrutinib increased with longer time on study treatment. The authors concluded that their data support the unprecedented single-agent activity of ibrutinib on overall response rate in patients with relapsed/refractory MCL. Results of this study, published in the *New England Journal of Medicine*, showed an estimated overall survival of 58% at 18 months (Figure 2).¹¹

Acknowledgment

Dr. Burger has received research funding from Pharmacyclics, Gilead, NOXXON Pharmaceuticals, and Sanofi.

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Clinical Trial Data on the BTK Pathway in B-Cell Malignancies

Adrian Wiestner, MD, PhD

Ibrutinib is a relatively selective BTK inhibitor. It acts primarily on BTK, but it also has effects on other kinases from the Tec family that have a cysteine in a crucial position (Figure 1).¹ Ibrutinib binds covalently to cysteine-481 in BTK and irreversibly inhibits the kinase. This mechanism permits once-daily oral dosing. Although the half-life of the drug is relatively short (approximately 4–8 hours), once-daily dosing is enough to continuously inhibit BTK for 24 hours.²

There have been several recent clinical trials of ibrutinib in B-cell malignancies. Advani and colleagues conducted the first phase I study, which enrolled patients with relapsed or refractory non-Hodgkin lymphoma, CLL, and Waldenström's macroglobulinemia from 8 centers in the United States.² The goal of this dose-escalation study was to establish a maximum tolerated dose or, in the absence of a dose-limiting toxicity, to define what dose of ibrutinib is required to fully inhibit BTK. The study enrolled 56 patients. Approximately 30% had follicular lymphoma (FL) and 30% had CLL/small lymphocytic

lymphoma (SLL). There were also patients with diffuse large B-cell lymphoma (DLBCL), Waldenström's macroglobulinemia, and marginal zone lymphoma.

No maximum tolerated dose was established, meaning that no dose-limiting toxicity was found. Overall, there was a very favorable adverse event profile. In this study, it was possible to measure the inhibition of BTK function based on an elegant assay. A probe that can detect an uninhibited BTK showed that ibrutinib, at a dose of 2.5 mg/kg, was able to completely block BTK with 95% or greater occupancy. The plasma level of the drug was maximized within 1–2 hours, and the terminal half-life was 48 hours. As mentioned previously, the inhibition of BTK persisted for 24 hours owing to irreversible inhibition. The overall response rate was 54% in an intention-to-treat analysis and 60% in the 50 evaluable patients. This activity is very exciting for a phase I study. Responses were seen across all histologies, with some differences in the actual rates. Among the 9 patients with MCL, there were 7 responses, including 3 complete responses (CRs). There were 11 responses among the 16 patients with CLL,

Table 1. Best Response to Therapy in a Phase II Trial of Ibrutinib in Relapsed or Refractory Mantle Cell Lymphoma*

Variable	No Prior Treatment With Bortezomib (n=63)	Prior Treatment With Bortezomib (n=48)	All Patients (N=111)
Response, n (%)			
Overall	43 (68)	32 (67)	75 (68)
Complete	12 (19)	11 (23)	23 (21)
Partial	31 (49)	21 (44)	52 (47)
None [†]	20 (32)	15 (31)	35 (32)
Response duration, months			
Median	15.8	NR	17.5
95% CI	5.6–NR	NR–NR	15.8–NR
Progression-free survival, months			
Median	7.4	16.6	13.9
95% CI	5.3–19.2	8.3–NR	7.0–NR
Overall survival, months			
Median	NR	NR	NR
95% CI	10.0–NR	11.9–NR	13.2–NR

CI=confidence interval; NR=not reached.

*Includes patients who received ibrutinib and had at least 1 efficacy assessment after baseline.

†Defined as stable or progressive disease.

Data from Wang ML et al. *N Engl J Med*. doi:10.1056/NEJMoa1306220.³

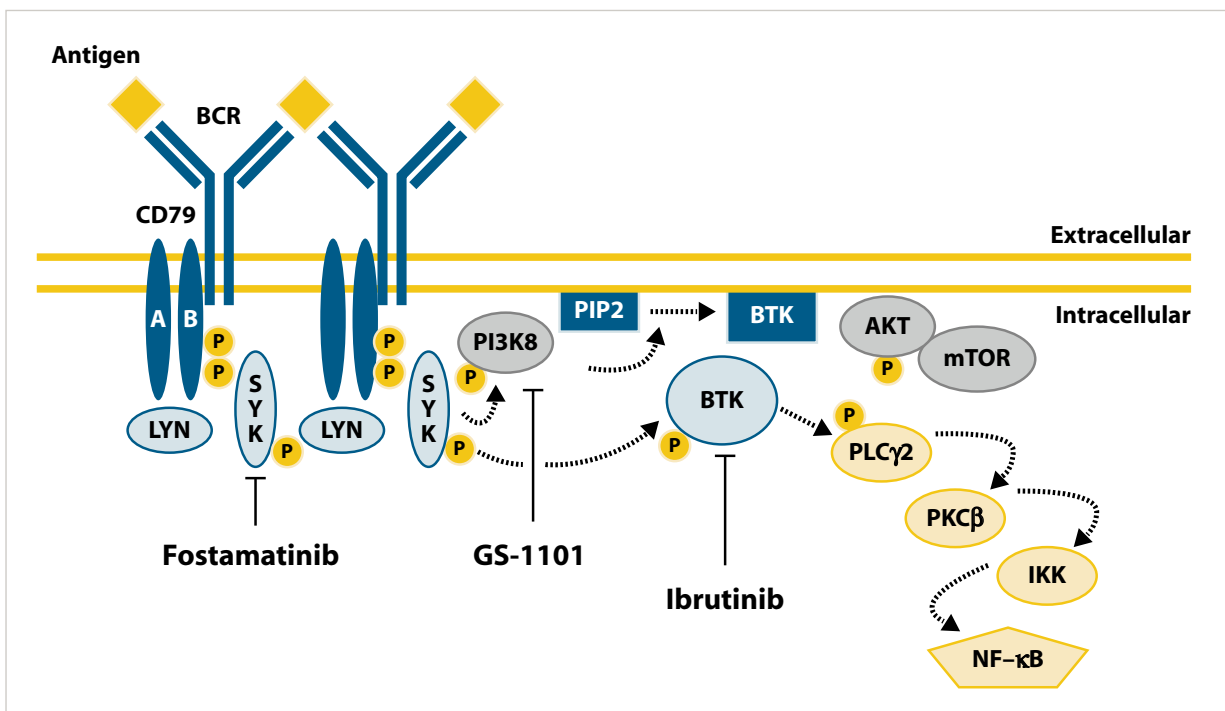


Figure 1. Antigen-dependent BCR signaling and its targeting by small-molecule inhibitors, such as ibrutinib. BCR=B-cell receptor; BTK=Bruton's tyrosine kinase. Reprinted with permission © 2013 American Society of Clinical Oncology. All rights reserved. Wiestner A. *J Clin Oncol*. 31(1), 2013:128-130.¹

including 3 CRs. Six of the 16 patients with FL responded. Responses were reported in 2 of 7 DLBCL patients and in 3 of 4 patients with Waldenström's macroglobulinemia.

Ibrutinib in MCL, CLL/SLL, FL, and DLBCL

In a phase I trial by Advani and colleagues in patients with relapsed/refractory B-cell malignancies, the highest response rates were seen in MCL and CLL/SLL.² In a phase II trial, Wang and associates examined the use of oral ibrutinib, at a dose of 560 mg/day, in patients with relapsed or refractory MCL.³ Patients were treated until progression. Cohort 1 enrolled 63 bortezomib-naïve patients, and cohort 2 enrolled 48 patients who had previously received bortezomib. The patients enrolled were representative of MCL overall: 45% had refractory disease, almost half were in the high-risk category, and many had already received very intense treatment regimens such as fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) or stem cell transplant.

The drug was well tolerated; most adverse events were grade 1 or 2. Overall, the most common nonhematologic adverse events were diarrhea (occurring in 50%), fatigue (41%), nausea (31%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper respiratory tract infection (23%), vomiting (23%), and decreased appetite (21%). Grade 3/4 hematologic adverse events included neutropenia (occurring in 16%), thrombocytopenia (11%), and anemia (10%). An adverse event led to discontinuation of therapy in 8 patients (7%). Among the 16 reported deaths (14%), 12 were caused by disease progression and 4 were caused by an adverse event (2 from pneumonia, 1 from sepsis, and 1 from a cardiac arrest that was considered unrelated to treatment).

The responses were remarkable. At a median follow-up of 15.3 months, the overall response rate was 68%, including 47% partial responses (PRs) and 21% CRs (Table 1). Notably, these responses actually improved with time. In a subset of 51 patients who had received treatment the longest, the CR rate was 37%. What is also remarkable is that the responses were seen across all traditional risk groups, such as patients who were refractory or who had been re-treated with multiple regimens and patients classified as high risk by the International Prognostic Index score. The time to CR ranged from 1.7 to 11.5 months. The median progression-free survival (PFS) was 13.9 months. The median duration of response and the overall response had not been reached.

A phase Ib/II study by Byrd and coworkers examined ibrutinib in CLL and SLL.⁴ Most of the patients in this study had high-risk disease. Ibrutinib was administered at 2 dosages: 420 mg/day (n=51) and 840 mg/day (n=34). There was no difference in efficacy between the 2 dose levels. The dose of 420 mg/day is now being used in other CLL studies. The patients enrolled were a good representa-

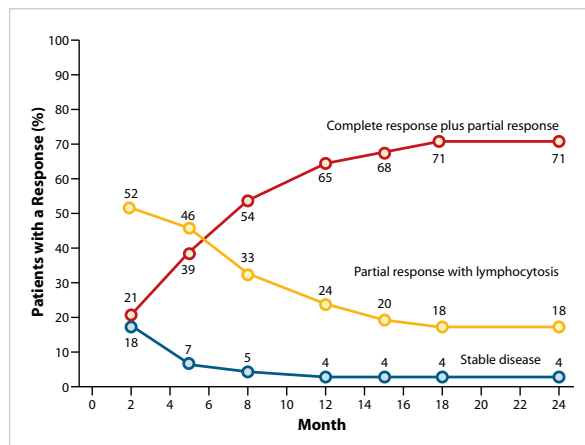


Figure 2. A phase Ib–II trial of ibrutinib in relapsed chronic lymphocytic leukemia used a criterion known as *partial response with lymphocytosis*, which refers to patients who had greater than 50% shrinkage of nodal disease and who fulfilled all criteria of partial response except for a persistent lymphocytosis. Adapted from Advani RH et al. *J Clin Oncol*. 2013;369(1):32-42.²

tion of CLL. Most patients (65%) had advanced disease. A substantial proportion of patients had adverse cytogenetic markers: 33% had deletion 17p and 35% had deletion 11q.

The adverse events were very similar to those reported in the MCL study. Most adverse events were grade 2 or lower. Overall, the most common reactions were diarrhea (49%), upper respiratory tract infection (33%), fatigue (32%), cough (31%), arthralgia (27%), rash (27%), and pyrexia (27%). Adverse events led to discontinuation of treatment in 2 patients in the 420-mg cohort (4%) and 4 patients in the 840-mg cohort (11%). Pneumonia (12%) and dehydration (6%) were the most frequent grade 3 or higher adverse events. Grade 3 or higher infections were most common early in the course of therapy.

Congenital BTK deficiency can lead to the immunodeficient state known as *agammaglobulinemia*, and a question had been raised regarding whether ibrutinib would induce hypogammaglobulinemia in patients. In the studies by Advani and colleagues and Byrd and coworkers, it appears that ibrutinib does not lower normal Ig levels.^{2,4} On the contrary, serum IgA levels seem to slightly increase with time.

The response rate was remarkably high in the study by Byrd and coworkers, at 71% for both dosages.⁴ A response was defined using the standard International Workshop on CLL (IWCLL) criteria that requires 50% shrinkage of nodal disease and a reduction of at least 50% in the lymphocyte count in the blood. A characteristic feature of ibrutinib is that it may transiently increase the peripheral lymphocyte count while the lymph nodes are shrinking and while the patients improve. This transient lymphocytosis is now understood to be an effect of redistributing parts of the disease into the blood. It is not a sign of progressive disease, and it has led to a reassessment of the standard response

criteria. There is now a response criterion known as *partial response with lymphocytosis*, which refers to patients who have greater than 50% shrinkage of nodal disease and who fulfill all criteria of PR except for a persistent lymphocytosis (Figure 2). The rates of PR with lymphocytosis were 20% in the 420-mg cohort and 15% in the 840-mg cohort. When the group achieving a PR with lymphocytosis was combined with the group achieving responses according to standard IWCLL criteria, the response rate was 91% for the 420-mg group and 86% in the 840-mg group. What is remarkable is that these responses were observed across all classic risk groups, including patients with high $\beta 2$ microglobulin, patients with advanced disease, patients with 17p or 11q deletions, and patients with bulky disease.

The PFS as estimated at 26 months was 75%. With longer follow-up, it is increasingly apparent that patients with 11q or 17p deletion have a somewhat higher rate of relapse or breakthrough during ongoing ibrutinib treatment. Patients with 17p deletion had a PFS at 26 months of 57%. The high response rate and benefit for patients with adverse CLL has been confirmed in additional studies. A study from the National Heart, Lung, and Blood Institute enrolled an elderly cohort and a cohort of patients with 17p deletion.⁵ The response rate, including PR with lymphocytosis, was more than 90% in both cohorts. Responses were durable, but the follow-up has been much shorter. The estimated PFS at 12 months was 94%, as presented at the American Association for Cancer Research meeting earlier in 2013.

Burger and coworkers presented an updated analysis of a phase II study of 40 previously treated, high-risk CLL patients treated with ibrutinib plus rituximab.⁶ Patients received ibrutinib (420 mg) for 12 cycles, plus rituximab (375 mg/m²) every week for 4 weeks (cycle 1), and then every 4 weeks for cycles 2–6. The analysis confirmed a very high response rate in these patients, who were selected for either being refractory to prior therapy or having the 17p deletion. The overall response rate was 83%, with an additional 8% of patients having PR with lymphocytosis.

So far, resistance to treatment appears not to be a major problem. However, relapses or breakthroughs are increased in the relapsed/refractory CLL cohorts. Importantly, Chang and colleagues identified mutations in BTK (C481S) in 4 CLL patients who developed resistance to ibrutinib.⁷ In 1 patient, a mutation in PLC $\gamma 2$ (R665W) was found. Although the rates of resistance and occurrence of these mutations appear to be low, it remains to be seen whether most patients will eventually relapse, or whether there is a subset of CLL patients who can be well treated with single-agent ibrutinib.

At the 2012 ASH meeting, Fowler and associates presented an updated analysis of the FL patients enrolled in the study by Advani and colleagues.^{2,8} As mentioned, the 16 FL patients in this phase I study received ibrutinib based on a dose-escalation protocol. Eleven of the patients received

ibrutinib at a dose of 2.5 mg/kg or higher and were evaluable for efficacy. The overall response rate in these 16 patients was 54%, including 3 CRs and 3 PRs. Again, the response rate improved with extended duration of treatment.^{2,8}

In the phase I study of ibrutinib by Advani and colleagues, there was a 29% overall response rate in DLBCL.² It is important to note that DLBCL comprises 2 distinct entities that can be considered different diseases: activated B-cell (ABC)-like DLBCL and germinal center B cell–like DLBCL. In ABC-like DLBCL, the cells are dependent on nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) pathway activation, which is initiated—at least in a subset of patients—by chronic active B-cell receptor signaling. In a subset of cases, this activation can be traced back to mutations in CD79A and CD79B, which encode parts of the B-cell receptor.

As can be seen in the results of the PYC-1106 study, presented by Wilson and associates, it is important to subdivide DLBCL patients based on their molecular signaling.⁹ This multicenter, phase II trial enrolled 70 patients with relapsed/refractory de novo DLBCL. None of the patients had transformed FL. Treatment consisted of ibrutinib at 560 mg/day until progression. The overall response rate across the entire group of DLBCL patients was 23%. When we look at the subgroups, 40% of the ABC-like DLBCL patients responded, whereas only 5% of the germinal-center B cell–like DLBCL patients responded ($P=.0126$). These results show that ibrutinib is selectively active in a disease characterized by a peculiar biology—the ABC-like lymphoma that has activation of the NF- κ B pathway. The study was further able to correlate mutations in specific signaling molecules with the likelihood of response to ibrutinib. In patients with a CD79B mutation, which enhances B-cell receptor signaling, the response rate was 60%. Responses to ibrutinib were also seen in all 4 patients with mutations in both CD79B and MYD88. Some patients have a mutation in MYD88 without any mutations in the B-cell receptor pathway. These patients were refractory to ibrutinib, showing that not only is it necessary to subdivide DLBCL, but it is also important to understand the mutational complement and the activation of distinct pathways within this biology to predict response to ibrutinib.

Summary

Ibrutinib is active across the spectrum of B-cell malignancies, indicating a type of non-oncogene addiction of B-cell malignancies to the B-cell receptor pathway. Ibrutinib was well tolerated across all the studies. Although there may be a small increased risk of infection with treatment, it appears that this risk is contributed mostly by the underlying disease and prior treatment. Responses were seen across all traditional

risk groups, including patients with refractory disease or 17p deletion. There was an increasing rate and depth of response with continued treatment. The duration of response was very encouraging, and in many instances, it is surpassing what has been achieved with standard options. Ibrutinib has been associated, particularly in CLL, with a characteristic transient lymphocytosis that is not a sign of progressive disease. It is necessary to adjust the response criteria so that these patients remain on-study while they are benefiting from the treatment. It will be important to design rational combination therapies for future studies that may have to be tailored to the specific B-cell malignancy treated.

Acknowledgment

Dr. Wiestner has no real or apparent conflicts of interest to report.

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Clinical Use of BTK Inhibitors

John C. Byrd, MD

It is an exciting time in the landscape of B-cell malignancies, particularly the low-grade B-cell malignancies: FL, MCL, Waldenström's macroglobulinemia, and CLL. For many years, the main treatment option was chemotherapy, which had no impact on survival. In 1997, the first targeted therapy, rituximab, was approved for the treatment of low-grade lymphoma.¹ Rituximab is used to treat all the B-cell lymphomas and CLL; it can prolong survival when combined with chemotherapy or administered as a single agent.

Rituximab may work in part through the same pathway as the BTK inhibitors. These agents began to be studied a little more than a decade after the introduction of rituximab. In 2007, idelalisib (GS-1101, formerly known as CAL-101), which inhibits PI3K/p110 δ , was entered into clinical trials.² Shortly thereafter, the first BTK inhibitor, ibrutinib, was entered into clinical trials for B-cell malignancies.³ There is a very bright future for these kinase inhibitors in B-cell malignancies; they may replace chemotherapy or potentially be integrated with

other biologic therapies, such as rituximab, ofatumumab, or other monoclonal antibodies.

The use of ibrutinib in B-cell malignancies has been studied in several clinical trials.⁴⁻⁹ It is expected that this agent will receive approval from the US Food and Drug Administration across a broad range of diseases, such as CLL, MCL, and Waldenström's macroglobulinemia in the relapsed setting. It may be some time before trials show efficacy in upfront therapy of CLL, MCL, and Waldenström's macroglobulinemia, but the available data have been equal to or better than those associated with the current best therapies for these B-cell malignancies. FL may be an exception because there are insufficient data to show whether ibrutinib will be as beneficial as idelalisib.¹⁰ It is probable that idelalisib will be used for relapsed FL sooner than ibrutinib, and it will be necessary to wait for more data to emerge with ibrutinib.

These agents will likely be used in relapsed disease—hopefully, first relapse and not beyond because it is clear from clinical trials that they work phenomenally well.

Table 1. Most Common Grade 1–4 Adverse Events Associated With Ibrutinib in a Phase Ib–II Trial of Chronic Lymphocytic Leukemia

Adverse Event	Grade 1–2, n (%)	Grade 3–4, n (%)	Total, n (%)
Diarrhea	40 (47)	2 (2)	42 (49)
Upper respiratory tract infection	28 (33)	0	28 (33)
Fatigue	24 (28)	3 (4)	27 (32)
Cough	26 (31)	0	26 (31)
Arthralgia	23 (27)	0	23 (27)
Rash	23 (27)	0	23 (27)
Pyrexia	19 (22)	4 (5)	23 (27)
Edema, peripheral	18 (21)	0	18 (21)
Muscle spasms	16 (19)	1 (1)	17 (20)
Constipation	14 (16)	1 (1)	15 (18)
Dizziness	14 (16)	1 (1)	15 (18)
Headache	14 (16)	1 (1)	15 (18)
Hypertension	11 (13)	4 (5)	15 (18)
Nausea	14 (16)	1 (1)	15 (18)
Sinusitis	11 (13)	4 (5)	15 (18)
Contusion	14 (16)	0	14 (16)
Vomiting	13 (15)	1 (1)	14 (16)
Neutropenia	0	13 (15)	13 (15)
Oropharyngeal pain	13 (15)	0	13 (15)

Data from Byrd JC et al. *N Engl J Med.* 2013;369(1):32-42.⁵

They are associated with stronger responses and are tolerated better in patients who have not received many lines of prior therapy, although there does not appear to be a difference in response duration based upon the number of prior therapies. There may be more toxicity in heavily treated patients, which reflects advanced disease states and the effects of prior therapies.

These agents are recognized to be very active. They induce durable remissions in CLL, MCL, and Waldenström's macroglobulinemia. These agents have very favorable toxicity profiles as compared with chemotherapy or chemoimmunotherapy. In general, late toxicities have not been observed. There are some complications, however, that are unique to these drugs. Infections were predicted, but the CLL experience has shown that, as patients take ibrutinib and their disease comes under control, the frequency of infections diminishes greatly over time. Patients are at the greatest risk of developing an infection within the first 6 months of therapy. The types of infection do not appear to be different from those usually seen in CLL. Ibrutinib has not been associated with the opportunistic infections that have been seen after fludarabine and bendamustine.

Patients receiving ibrutinib may experience rash and loose stools, which typically last for the first 2 months of treatment and resolve without treatment (Table 1).⁵ If this reaction does not resolve, it may be necessary to decrease the dose of ibrutinib. Arthralgias are seen in approximately 10–20% of patients, particularly those who are younger, as they respond to treatment. It has been suggested that the arthralgias occur because the patients are becoming more active. Arthralgias are easily managed with acetaminophen or nonsteroidal anti-inflammatory agents.

The most concerning side effect with ibrutinib is the potential for bleeding and bruising. It is not known why these events occur. The risk is higher in patients who are receiving warfarin; these patients have some unusual bleeding complications, such as subdural hematomas. Patients who are receiving warfarin based on a high risk of thromboembolic events are not appropriate candidates for ibrutinib until there is a better understanding of the pathophysiology of why these adverse events occur. Patients with CLL or Waldenström's macroglobulinemia who are receiving ibrutinib might initially benefit from idelalisib when this drug is approved based upon its position in the proximal signaling pathway, provided downstream activating mutations are not the source of resistance to ibrutinib.

Patients receiving ibrutinib are not likely to relapse until 6–12 months. In some studies, follow-up is beyond 2 years, and the number of CLL and MCL patients remaining in remission is still very favorable. Some patients are relapsing, but many are not. This observation raises several questions: Will drug resistance emerge, and in which patients? How can it be prevented? Data that will shed light on these questions are just now starting to become available, and they will be factored into the development of combination strategies, perhaps with agents such as ABT-199, which inhibits BCL-2, or monoclonal antibodies, in order to induce deep remissions. Another question is whether there will be patients who can be maintained on these drugs for the long-term. These agents are highly effective, but they will likely increase healthcare system costs if patients receive them for extended periods of time.

It will likely be necessary to revise ideas about treatment of these diseases. When a patient is treated with chemotherapy, the presence of residual disease that persists in the blood or bone marrow almost always suggests that the disease is going to come back quickly. In contrast, with agents such as ibrutinib, there currently does not appear to be such a correlation. The CR rate with ibrutinib is relatively low; however, the patients remain in remission. It will be important to continue observing patients to see whether the presence of minimal residual disease becomes important with more extended follow-up. Particularly for CLL, ibrutinib is a remarkable drug. With traditional

treatments, when lymphocytes appear in the blood, they typically do not disappear and necessitate additional treatment. In contrast, with ibrutinib, the patients with lymphocytosis are the ones with the best responses. Treatment of CLL, MCL, and Waldenström's macroglobulinemia is going to change very significantly, and many of our patients may be able to avoid chemotherapy.

Acknowledgment

Dr. Byrd has received support for running clinical trials related to ibrutinib. He is an unpaid consultant for Pharmacyclics. Dr. Byrd has received royalties related to prior work done with GS-1101, but the proceeds have been contractually committed to charity.

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The Importance of the BTK Pathway in B-Cell Malignancies: Discussion

John C. Byrd, MD, Jan A. Burger, MD, PhD, and Adrian Wiestner, MD, PhD

John C. Byrd, MD Dr. Burger, what do you think will be the next big questions regarding the use of novel agents in B-cell malignancies?

Jan A. Burger, MD, PhD I think one of the major questions will be how to manage patients who develop resistance. Although the numbers are very small, my impression from having patients on these trials for the past 3 years is that the annual relapse rate seems to be less than 5%. However, the more widely these drugs are used, the more cases of resistance will be seen. The hope is that, for example, patients who become resistant to the PI3 kinase inhibitors can receive rescue therapy with a BTK inhibitor, or the other way around. That direction can be foreseen from the experience in chronic myeloid leukemia, where different second-generation kinase inhibitors have been used to rescue patients who failed to respond at some point to treatment with imatinib. No formal studies have examined this approach, but I expect they will in

the future. At the same time, there will be a major effort to understand resistance mechanisms. These mechanisms could be related to mutations that make the drugs bind less effectively to the target or to mutations in the kinase domains.

The other major area is the long-term safety concerns in terms of immunity. The experience to date has not shown the emergence of opportunistic infections. That is a very pleasant surprise, although we may still need to explore how to address vaccinations once patients are on these kinase inhibitors, like ibrutinib. Can these patients mount immunity towards vaccines? This question will be actively explored.

John C. Byrd, MD Dr. Wiestner, what do you see as the next big questions for these compounds?

Adrian Wiestner, MD, PhD One key question is resistance. Another is how to include ibrutinib in combination with other agents. It will be important to determine

how to formulate curative combinations using ibrutinib or another kinase inhibitor as the backbone.

How do we redesign a regimen with a curative intent? It will be necessary to rearrange our thinking. Understanding mechanisms of resistance will be important for designing these combinations. Seeing that ibrutinib has such an impressive spectrum of activity, and may offer a chemotherapy-free approach for indolent B-cell malignancies, I am not enthusiastic about trials that are combining this agent with chemotherapy in patients with these diseases. In contrast, combinations of ibrutinib with chemotherapy might be a key to increase the rate of cure in aggressive lymphomas. Thinking about novel combinations, there is the potential for ibrutinib to be combined with ABT-199, a drug that directly targets the apoptotic machinery in B cells; with immunostimulatory agents; or with immunotherapy approaches, such as monoclonal antibodies, chimeric antigen receptor (CAR) T-cells, or vaccines. These approaches will require thinking outside the box of what we learned with classic chemotherapy.

John C. Byrd, MD I would agree that with this class of drugs, it will be necessary to think outside the box. There are 2 critical topics of focus. First, what is the actual target? Second, what are the alternative targets of ibrutinib—other than BTK—and how do these targets contribute to ibrutinib's clinical activity? The preclinical studies of several groups show that, in mouse models of

CLL, BTK is important to the pathogenesis of the disease. However, there are also alternative targets, such as IL-2-inducible T-cell kinase (ITK), which we know is inhibited by ibrutinib and is important to Th2 T cells. Potentially, while ibrutinib suppresses B-cell function, it may actually enhance T-cell function.

Perhaps one of the most exciting possibilities with ibrutinib may be its use in combination with other agents, such as the first clinically applicable ITK inhibitor; other T-cell therapies, such as the CAR T cells; and PD-1 antibodies or CTLA-4. These untested combinations may even allow us to extend the use of ibrutinib outside of the diseases where it has high responses. We are really at an incredibly exciting time in our field. We are making the leap from a treatment that is palliative, but which has not been shown to have any potential to improve survival in these diseases, to new treatments that will bring meaningful improvements in patient outcomes.

Acknowledgments

Dr. Byrd has received support for running clinical trials related to ibrutinib. He is an unpaid consultant for Pharmacyclics. Dr. Byrd has received royalties related to prior work done with GS-1101, but the proceeds have been contractually committed to charity. Dr. Burger has received research funding from Pharmacyclics, Gilead, NOXXON Pharmaceuticals, and Sanofi. Dr. Wiestner has no real or apparent conflicts of interest to report.

Slide Library

Bruton's Tyrosine Kinase (BTK)

- Most well known for its role in the B-cell receptor signaling pathway
- Transmits signals from the cell surface to the cytoplasm and into the nucleus. Activation of this pathway ultimately results in the survival and expansion of both normal and malignant B cells
- In normal B cells, the function of the pathway is to select antigen-specific B cells. In lymphatic tissues, after these cells are selected by the antigen, they expand in concert with other signals from the microenvironment, which includes T cells and other cells.

B-Cell Receptor Signaling in B-Cell Malignancies

- It is thought that the function of the B-cell receptor signaling pathway in B-cell malignancies is similar to its activity in normal B cells, and that it helps the neoplastic B cells in lymphoma patients and B-cell leukemia patients survive and expand
- Gene expression profiling has shown that molecules in the B-cell receptor signaling pathway are activated in areas where CLL cells are growing, which—similar to normal B-cell biology—is mostly in lymphatic tissues¹
- The B-cell receptor signaling pathway seems to be critical for the survival of certain B-cell lymphomas²

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BTK in B-Cell Function

- It has become clear that BTK plays a major role in B-cell function
- BTK is a major intermediary in B-cell receptor signaling, and it was recognized within the last decade as a therapeutic target
- Several agents that target this enzyme are in development
- The lead compound, ibrutinib, is in phase III clinical trials in patients with CLL, mantle cell lymphoma, and Waldenström's macroglobulinemia

BTK in CLL

- The strongest signal in terms of BTK activity is in CLL. The cells in this disease divide and are activated in the lymphatic tissues, where they receive signals that activate the B-cell receptor. There may also be autoactivation of the B-cell receptor in these areas
- The clinical response to BTK inhibition is characterized by initial lymphocytosis in which the CLL cells are redistributed from the lymphatic tissues into the bloodstream, resulting in rapid shrinkage of lymph nodes
- Other sites of disease infiltration, like the spleen, also resolve very quickly

Ibrutinib

- Ibrutinib is a relatively selective BTK inhibitor
- It acts primarily on BTK, but it also affects other kinases from the Tec family that have a cysteine in a crucial position¹
- Ibrutinib binds covalently to cysteine-481 in BTK and irreversibly inhibits the kinase. This mechanism permits once-daily oral dosing, even with the drug's relatively short half-life of approximately 4-8 hours²

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 2. Warden R, et al. *J Clin Oncol* 2012;30(15):1788-1795.

Ibrutinib in Relapsed/Refractory Mantle Cell Lymphoma: Phase II Data¹

- At a median follow-up of 15.3 months, the overall response rate was 68%, including 47% PRs and 21% CRs. These responses improved with time
- In a subset of 51 patients who had received treatment the longest, the CR rate was 37%
- The responses were seen across all traditional risk groups
- The time to CR ranged from 1.7 months to 11.5 months
- The median PFS was 13.9 months
- Most adverse events were grade 1 or 2

1. Wang M, et al. *Topical BTK with ibrutinib is critical to cells that maintain cell lymphoma (submitted)*. *ASCO Meeting Abstracts* 2013;31(15):4502.

Ibrutinib in CLL and SLL: Phase Ib/II Data¹

- The response rate was 71% for the 2 dosing cohorts: 420 mg/day and 840 mg/day
- The rates of PR with lymphocytosis were 20% in the 420-mg cohort and 15% in the 840-mg cohort
- The PFS as estimated at 26 months was 75%
- Most adverse events were grade 2 or lower

1. Byrd D, et al. Blood. 2012;120(11):2240.

Ibrutinib in High-Risk CLL: Phase II Data¹

- A study from the National Heart, Lung, and Blood Institute enrolled an elderly CLL cohort and a cohort of CLL patients with 17p deletion
- The response rate, including PR with lymphocytosis, was more than 90% in both cohorts
- The estimated PFS at 12 months was 94%

1. Wenzel K, et al. Paper presented at Annual Meeting of the American Association for Cancer Research, April 9-13, 2012, Washington, DC, Abstract 30141.

Ibrutinib in Relapsed/Refractory De Novo DLBCL: Phase II Data¹

- The overall response rate across the entire group of DLBCL patients was 23%
- Subgroup analysis showed that 45% of the ABC-like DLBCL patients responded, whereas only 5% of the germinal-center B cell-like DLBCL patients responded
- These results show that ibrutinib is selectively active in a disease characterized by a peculiar biology—the ABC-like lymphoma that has activation of the NF- κ B pathway

1. Byrd D, et al. Blood. 2012;120(11):2240.

Management of Adverse Events Associated With Ibrutinib

- Patients may experience rash and loose stools, which typically last for the first 2 months of treatment and resolve without treatment. If this reaction does not resolve, it may be necessary to decrease the dose of ibrutinib.
- Arthralgias are seen in approximately 10–20% of patients, particularly those who are younger, as they respond to treatment. Arthralgias are easily managed with acetaminophen or nonsteroidal anti-inflammatory agents.
- There is a potential for bleeding and bruising. The risk is higher in patients who are receiving warfarin, and therefore such patients are not appropriate candidates for ibrutinib until there is a better understanding of the pathophysiology of why these adverse events occur.

1. Byrd D, et al. Blood. 2012;120(11):2240.

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