

# Dawn of a new era: targeting the B-cell receptor signaling pathway to conquer B-cell lymphomas

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Despite the advent of modern chemo- and radio-immunotherapies, the disease course in most mature B-cell malignancies (with the exception of diffuse large B-cell lymphoma [DLBCL] and Burkitt lymphoma) is highlighted by frequent relapses, progressively shorter remissions, and eventual emergence of therapy resistance. An effective salvage therapy in this setting remains an area of unmet medical need. Bruton's tyrosine kinase (BTK) is a critical component of B-cell-receptor signaling that mediates interactions with the tumor microenvironment and promotes survival and proliferation of malignant B-cells.<sup>1,2</sup> The BTK protein itself is a Tec family tyrosine kinase that is activated by spleen tyrosine kinase following B-cell-receptor stimulation and which is then required for downstream events including calcium release, activation of the NF $\kappa$ B and NFAT pathways, cell survival and proliferation.<sup>1</sup> The fundamental role of BTK in B-cell function is underscored by the human disease X-linked agammaglobulinemia, which is caused by loss of function mutations in BTK.<sup>3</sup> These mutations result in the virtual absence of all B cells and immunoglobulins, leading to recurrent bacterial infections. Ibrutinib (formally known as PCI-32765) is the first-in-class BTK inhibitor to enter clinical trials. In a multicenter phase 1 dose-escalating study, 56 patients with relapsed or refractory B-cell lymphomas received escalated doses of oral ibrutinib either on an intermittent or continuous daily dosing schedule.<sup>4</sup> The most common adverse effects were grade 1-2 nonhematologic toxicities, which included rash, nausea, fatigue, diarrhea, muscle spasms/myalgia, and arthralgia. An overall response rate (ORR) of 60% was achieved across all histological types with the best efficacy seen in patients with mantle cell lymphoma (MCL; 78%) and chronic lymphocytic leukemia (CLL; 68%). While

both intermittent and continuous dosing schedules demonstrated efficacy, the study favored continuous dosing for future trials. Two recent key trials providing further proof of the remarkable activity of BTK inhibitors in CLL<sup>5</sup> and MCL<sup>6</sup> are discussed in the Community Translations section of this issue on page XXX.

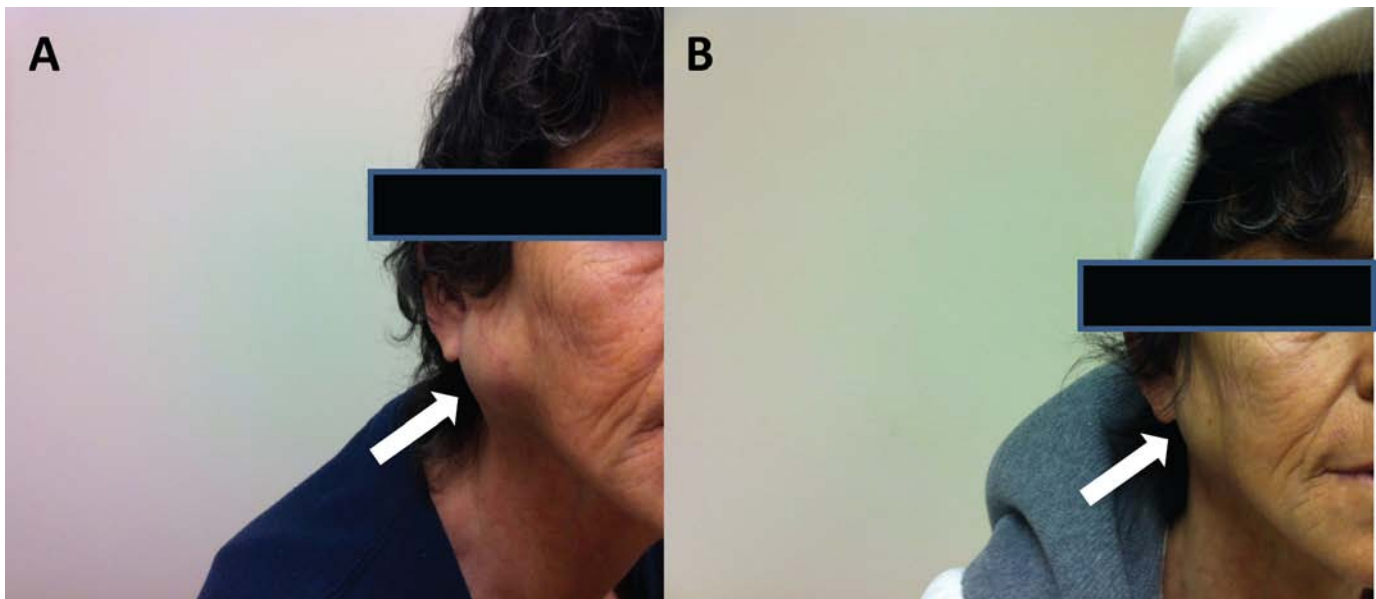
In the study, the investigators reported high ORRs (about 70%) with single-agent ibrutinib in patients with relapsed or refractory CLL.<sup>5</sup> Perhaps the most important finding of this study is the encouraging activity of this agent in patients with high-risk features historically associated with a dismal prognosis, such as chromosome 17p deletion and unmutated immunoglobulin variable-region heavy chain (IgVH) gene status. The ORR was 68% in the 17p deleted patients and 77% in those with unmutated IgVH gene. These responses appear durable. At 26 months, the estimated progression-free survival (PFS) was 75% and overall survival (OS) was 83%. Typically in CLL patients, an increase in peripheral blood lymphocytosis during therapy is considered a sign of disease progression. A unique feature of ibrutinib treatment in CLL patients is the rapid resolution of enlarged lymph nodes along with a transient surge in peripheral blood lymphocytosis, likely mediated by inhibition of cell adhesion.<sup>6</sup> Treating physicians will need to be aware of this phenomenon with ibrutinib therapy so as not to confuse it with disease progression. The safety profile of ibrutinib appears favorable; however the possible risk of bleeding complications with this agent warrants further investigation. Seven patients in this study developed Richter's transformation.<sup>5</sup> It is not known whether ibrutinib promotes histologic transformation by altering tumor microenvironment. The key clinical question focuses on how these results will impact our practice in the coming years.

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**Disclosures** The authors have no disclosures.

Commun Oncol 2013;10:279-281  
DOI: 10.12788/j.cmonc.0066

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**FIGURE 1** A, A heavily pretreated mantle cell lymphoma patient at baseline with large parotid mass. B, Significant decrease in mass after 4 weeks of ibrutinib therapy.

If durable remissions with ibrutinib in CLL patients in general and high-risk patient in particular are confirmed, then this will certainly lead us to reappraise the role of allogeneic transplantation for this disease. In fact, some centers where ibrutinib is available on clinical trials have anecdotally seen a decrease in the number of CLL patients requiring allogeneic transplant (Steven M. Devine; personal communication). Several ongoing trials will clarify the role of ibrutinib (either alone or in combination) for both patients with relapsed or refractory disease (RESONATE-1, a phase 3 study of ibrutinib versus ofatumumab; and HELIOS, a trial of bendamustine plus rituximab, with or without ibrutinib) and in therapy naïve patients (RESONATE-2 trial, a phase 3 study of ibrutinib compared with chlorambucil).

In the second study, the investigators reported remarkable efficacy (ORR, 68%) and prolonged remissions with ibrutinib monotherapy in 111 patients with relapsed or refractory MCL.<sup>6</sup> After a median follow-up of 15.3 months, the median PFS was 13.9 months, and median OS was not reached. These findings are noteworthy because relapsed MCL has a grim prognosis and is without curative options (eg, allogeneic transplantation), the survival beyond 12-24 months is unusual. In fact in our Myeloma and Lymphoma Program at West Virginia University we have seen dramatic responses to ibrutinib therapy in heavily pretreated MCL patients enrolled in ongoing clinical trials (Figure 1). On the basis of these efficacy data, ibrutinib was given breakthrough therapy

designation by the Food and Drug Administration in early 2013 for patients with relapsed or refractory MCL. Currently, a registration trial (RAY) of ibrutinib and temsirolimus has been initiated in the relapsed or refractory setting, and the SHINE study of bendamustine plus rituximab with or without ibrutinib in newly diagnosed, elderly patients has started patient accrual.

BTK inhibitors are likely going to change the landscape of lymphoma and leukemia therapeutics. In fact, trials evaluating the role of ibrutinib in relapsed follicular lymphoma (the DAWN study) and newly diagnosed nongerminal center DLBCL (PHOENIX trial) are underway. Beyond mature B-cell neoplasms, it is conceivable that BTK inhibitors will be evaluated in other B-cell-mediated disorders including autoimmune diseases, immune thrombocytopenic purpura, chronic graft-versus-host disease. The BMT-CTN cooperative group is planning to evaluate ibrutinib maintenance therapy after autologous transplantation in DLBCL. Several other BTK inhibitors are also entering preclinical and clinical testing (eg, GDC-0834, RN-486, CC-292, ONO-4059). Although BTK inhibitors are at the brink of providing clinicians another promising agent to their therapeutic armamentarium, our quest for finding curative therapies in lymphoid malignancies continues. I also remain mindful of steep costs of new targeted therapies, and although these projections for ibrutinib are not yet available, judging by the current cost trends of other oral targeted agents,

ibrutinib will likely be an efficacious, but expensive option.

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