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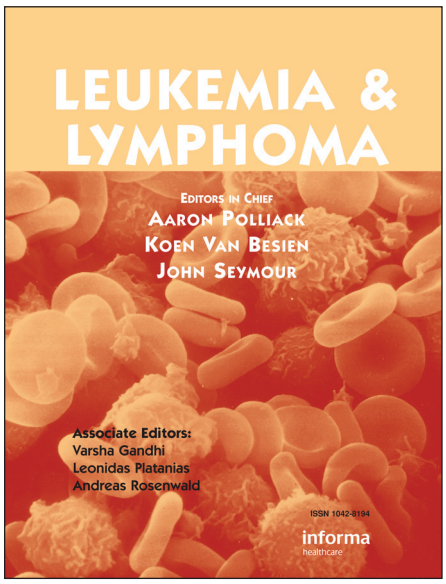

Emerging drug profiles: Bruton tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765

Jan A. Burger, and Joseph J. Buggy

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Abstract

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Emerging drug profiles: Bruton tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765)

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Abstract

Over the past 3 years, ibrutinib (PCI-32765) has emerged as a breakthrough in targeted therapy for patients with certain types of B cell malignancies. Early stage clinical trials found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), providing the rationale for ongoing Phase 3 trials. In contrast to conventional chemo-immunotherapy, ibrutinib is not myelo-suppressive, and responses are not affected by disease features that predict failure to respond to or short remission durations after chemo-immunotherapy, such as del17p. In CLL, ibrutinib characteristically causes an early redistribution of tissue-resident CLL cells into the blood, with rapid resolution of enlarged lymph nodes, along with a surge in lymphocytosis. Later, after weeks to months of continuous ibrutinib therapy, the growth- and survival-inhibitory activities of ibrutinib result in the normalization of lymphocyte counts and remissions in a majority of patients. This review discusses the discovery, preclinical and clinical development of ibrutinib, its pathophysiological basis, and outlines perspectives for future use of ibrutinib.

Key Words: Chronic lymphocytic leukemia, CLL, microenvironment, B cell receptor, BCR, BTK, ibrutinib

Rationale for targeting BTK

BTK is a non-receptor tyrosine kinase of the Tec kinase family, and plays a central role in B cell receptor (BCR) signaling. Upon BCR activation, BTK becomes activated by other tyrosine kinases, such as Lyn and SYK, resulting in activation of transcription factors necessary for B-cell proliferation and differentiation[1]. In addition to its role in BCR signaling, BTK also is involved in signaling of receptors related to B cell migration and adhesion, such as the CXCR4 and CXCR5 chemokine receptors and adhesion molecules (integrins)[2-4] (Figure 1).

BTK is primarily expressed in hematopoietic cells, particularly in B cells, but not in T cells or normal plasma cells[5]. BTK is of critical importance for B cell development, as demonstrated by the absence of blood B cells in patients with X-linked agammaglobulinemia (XLA), and reduced mature B cell numbers in the murine counterpart, X-linked immunodeficiency (xid). Both XLA and xid result from deficient BTK function due to functional null BTK mutations[6-8]. The primary immunodeficiency XLA is characterized by low serum immunoglobulin levels and lack of peripheral B cells, and generally becomes symptomatic in boys with opportunistic infections during the first 2 years of life, after the protective maternal antibodies have vanished[9]. Because of its prominent role in B cell development and function, BTK became the target for drug development with small molecule inhibitors and application in various diseases, mostly in autoimmune diseases, such as rheumatoid arthritis (RA)[10-12] and B cell malignancies[13-15].

BTK in the BCR signaling pathway in normal and malignant B cells

BCR activation can be induced by antigen or can be ligand-independent ("tonic" BCR signaling), and it activates a cascade of signaling events that cause normal B cell selection, proliferation, differentiation, and antibody production. Thereby, BCR signaling allows for the expansion of selected, antigen-specific B cells, and deletion of unwanted, self-reactive B cells[16,17]. In B cell malignancies, such as chronic lymphocytic leukemia(CLL)[18-20] and diffuse large cell B cell lymphoma (DLBCL)[21], BCR signaling is increasingly recognized as a key mechanism that promotes disease progression, even though the precise mechanism of BCR stimulation and the nature of the antigens that can activate the BCR are controversial[22-24]. In B cell malignancies, the BCR signaling pathway can be activated in an antigen-independent fashion, for example via activating mutations in CD79a and CD79b in subtypes of DLBCL[21]. In CLL, on the other hand, BCR pathway activation appears to be antigen-dependent[24], and induced by microbial[25] or autoantigens, such as vimentin[26], myosin[27], or rheumatoid factors[28,29]. A recent study raised the additional, alternative possibility of ligand-independent BCR signaling in CLL as a result of self-recognition of an intrinsic **IGHV** motif[23]. Additional evidence for the importance of BCR signaling in CLL comes from recent comparative gene expression profiling (GEP) data that revealed

BCR signaling as the most prominent pathway activated in CLL cells isolated from areas of proliferation within the lymphatic tissues[30].

The BCR is composed of an antigen-specific membrane Ig paired with Ig-α/Ig-β hetero-dimers (CD79a/CD79b). Engagement of BCRs by antigen induces phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAM) in the cytoplasmatic tails of CD79a and b[31] by Lyn and other Src family kinases (Fyn, BLK), which also activate BTK, and PI3K (Figure 1). These events are associated with BCR oligomerization and BCR microcluster growth, leading to the recruitment and activation of SYK [32]. Upon phosphorylation, SYK, BTK, and PI3K activate downstream signaling pathways, including calcium mobilization and activation of AKT kinase, extracellular signal-related kinase 1/2 (ERK, also called p44/42 mitogen-activated protein kinase/MAPK),and nuclear factor kappa B (NF-κB).)[33,34]. The clinical success of small molecule inhibitors of BCR-associated kinases in CLL patients in early stage clinical trials[15,35] suggests that the BCR signaling may be the “Achilles’ heel” of CLL.

Ibrutinib: discovery, pre-clinical development, and structure

Development of therapeutic kinase inhibitors has largely been focused on ATP-competitive compounds that target the ATP binding site of protein kinases[36]. However, key challenges in the development of such kinase inhibitors have been relatively poor selectivity, and binding site competition due to high concentrations of endogenous ATP substrate. Covalent, irreversible inhibitors address these challenges, because they exhibit high selectivity, prolonged pharmacodynamics, and potency in overcoming endogenous ATP competition[37]. In 2007, scientists from Celera Genomics reported a structure-based approach for creating a series of small molecules that inactivate BTK through irreversible covalent bonding to Cys-481 in the ATP binding domain of BTK (Figure 2, 3)[38]. The investigation of this compound series began with a reversible 1-cyclopentyl-4-aminopyrazolo[3,4-*d*]pyrimidine core structure with a diphenyl ether that provided high activity against BTK and the Src-family kinases. The cyclopentyl was replaced by 3-piperidyl, which then was substituted with an acrylamide warhead which acts as a Michael acceptor for covalent bonding to the target Cys-481 in BTK[37,38]. In April 2006, Pharmacyclics had acquired Celera’s small molecule BTK inhibitor discovery program. This included a series of compounds initially generated as proof-of-concept or “tool” compounds. One of these compounds, PCI-32765 (Celera’s compound 13) was subsequently chosen for further preclinical development (the chemical structure is displayed in Figure 2).

The BTK inhibitor programs at Celera and Pharmacyclics initially were driven by the desire to develop novel targeted therapeutics for patients with rheumatoid arthritis (RA), and consequently, these BTK inhibitors were initially tested in RA in vivo models[10,38]. Later, PCI-32765 was chosen as a development candidate due to its remarkable nonclinical safety and efficacy in both lymphoma and autoimmune models[10]. PCI-32765 was selected for studies by Pharmacyclics because of its

potency (IC_{50}, 0.5 nM) and selectivity for BTK in a screening panel of kinases [10]. Only a small subset of tyrosine kinases in the human genome is predicted to contain a modifiable cysteine residue homologous to Cys-481 in BTK, and only this subset is thought to be susceptible to irreversible and durable inhibition by ibrutinib. The Cys-containing kinases include EGFR (IC_{50} = 12 nM), HER2 (IC_{50} = 22 nM), HER4 (IC_{50} = 0.6 nM), ITK (IC_{50} = 12 nM), BMX (IC_{50} = 1 nM), JAK3 (IC_{50} = 22 nM), TEC (IC_{50} = 1 nM) and BLK (IC_{50} = 1 nM). The extent to which inhibition of one or more of these alternate kinases contributes to the efficacy or toxicity of ibrutinib is not known. Ibrutinib also has reversible inhibitory activity against other kinases that do not contain a Cys-481 homolog, and several of these have been defined[10]. However, any such reversible kinase inhibition is likely to be short-lived in vivo, since the effective half-life of ibrutinib following oral dosing in humans is only 2 to 3 hours (as measured post time to maximum concentration [T_{max}] to 6 hours). Thus, by combining fast irreversible binding to BTK with rapid in vivo elimination, ibrutinib provides a unique approach to improve selectivity for BTK in vivo relative to reversibly inhibited off target kinases. In cell assays, ibrutinib potently inhibited phosphorylation of BTK in a B cell line (IC_{50}, 11 nM) as well as the downstream substrates PLCγ and ERK. Ibrutinib also potently inhibited the ability of primary human B cells to become activated following stimulation at the BCR.

PCI-32765 was assigned the International Nonproprietary Name (INN) and United States Adopted Name (USAN) of “ibrutinib” by the World Health Organization and USAN Council, respectively. The molecular formula of ibrutinib is $C_{25}H_{24}N_6O_2$, its molecular weight is 440.5 g/mol, and its chemical name is 1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one. Currently, ibrutinib is under late stage clinical development by Pharmacyclics and Johnson & Johnson's Janssen Biotech, Inc. division for chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM).

Development of ibrutinib in B cell malignancies

The in vivo activity of ibrutinib in B cell lymphoma was first demonstrated in spontaneous canine B-cell lymphomas, where ibrutinib was administered orally and induced responses in 3 out of 8 dogs[10]. Herman *et al*. reported that ibrutinib induced CLL cell apoptosis in the presence of pro-survival factors (CD40L, BAFF, IL-6, IL-4, TNF-α, fibronectin, stromal cell contact)[13]. Ponader *et al* reported that ibrutinib inhibits CLL cell survival and proliferation, as well as leukemia cell migration towards the tissue homing chemokines CXCL12 and CXCL13[14]. We also found that ibrutinib downregulated secretion of BCR-dependent chemokines (CCL3, CCL4) in vitro and in CLL patients receiving ibrutinib. Furthermore, ibrutinib effectively thwarted disease progression in the TCL-1 mouse model of CLL[14]. De Rooij and colleagues reported ibrutinib’s interference with CLL cell chemotaxis and integrin-mediated CLL cell adhesion[39], suggesting that these BCR-independent actions of ibrutinib explain the redistribution of CLL cells from the tissues into the

peripheral blood. Further insight into mechanism of action of ibrutinib in CLL came from a study by Schwamb et al., which reported that ibrutinib inhibits BCR-dependent UDP-glucose ceramide glucosyltransferase expression and thereby sensitized CLL cells to apoptosis[40].In DLBCL, ibrutinib demonstrated selective toxicity in cell lines with chronic active BCR signaling[21], it down regulates IRF4, and synergizes with lenalidomide in killing of activated B cell-like (ABC) subtype DLBCL cells[41]. In multiple myeloma (MM) models, ibrutinib inhibited RANKL/M-CSF-induced phosphorylation of BTK and downstream signaling in osteoclasts (OC), resulting in diminished bone resorption. Ibrutinib also inhibited secretion of cytokines and chemokines from OC and stromal cells, CXCL12-induced migration of MM cells, IL-6- and stroma-supported growth of MM cells, and in vivo MM cell growth and MM cell-induced osteolysis of implanted human bone chips in SCID mice[42].

The most mature clinical data about effects of ibrutinib on B cell malignancies are available for patients with CLL, MCL, and DLBCL[15]. For CLL, ibrutinib is given orally as a once-daily fixed dose of 420 mg on a continuous schedule until progression or toxicity. At this dose, ibrutinib induces full BTK target occupancy, based on probe (fluorescently tagged derivative of ibrutinib) assays of peripheral blood mononuclear cell (PBMC) samples from CLL patients treated with ibrutinib[15]. Ibrutinib is both rapidly absorbed and rapidly eliminated after oral administration. The effective half-life of PCI-32765 following oral dosing in humans is 2 to 3 hours (as measured post time to maximum concentration [T_{max}] to 6 hours). Despite such rapid clearance from plasma, BTK remained covalently bound to ibrutinib for at least 24 hours. This brief daily exposure to drug in plasma limits the duration of off-target effects and this may account for the promising safety profile of ibrutinib reported to date.

In CLL patients, ibrutinib induces lymphocytosis during the first weeks of therapy, which is variable among patients and directly related to the presence of the drug. When ibrutinib was given in an intermittent fashion with a monthly 7-days-off-drug period, a saw-toothed pattern of absolute lymphocyte counts (ALC) was noticed, where ALC rapidly dropped during the off-drug period, and then increased again, once ibrutinib was re-started[15]. This lymphocytosis is asymptomatic, transient, and resolves in most patients during the first few months of therapy. It is due to the re-distribution of CLL cells from the tissue compartments into the peripheral blood[15,43] and therefore must not be confused with lymphocytosis due to disease progression[44]. Interestingly, this redistribution phenomenon in CLL patients is not restricted to ibrutinib, and appears to be a class effect of kinase inhibitors interfering with the BCR and chemokine signaling pathways. Similar clinical effects have been reported for the spleen tyrosine kinase (SYK) inhibitor fostamatinib (R406/R788)[35] and the PI3Kδ inhibitor GS-1101[45]. This effect has prompted experts in the CLL field to re-evaluate current response guidelines to accomodate treatment-related lymphocytosis.

In an analysis presented at the 2012 American Society of Hematology (ASH) meeting, Byrd et al. reported that single-agent ibrutinib induces an overall response

rate (ORR) of 68% (10% CR, 58% PR) in previously untreated CLL patients aged 65 or older (n=31) and an ORR of 71% (2% CR, 68% PR) in previously treated CLL patients (n=85)[46]. These data are based on relatively long follow-up in the untreated and previously treated groups (median time on treatment: 20.3 and 20.89 months, respectively with an estimated PFS of 96% and 75%, respectively). In MCL, Wang and colleagues reported about an ORR of 65% in bortezomib-naïve MCL patients (n=63) and an ORR of 72% in bortezomib-exposed patients (n=47)[47]. With additional follow up, there was an increase in complete response rate over time, and response appear to be durable. In follicular lymphoma (FL), and DLBCL, there are limited clinical data available, but the published data[15] and conference presentations of ongoing early stage clinical trials in these other B cell malignancies highlight promising activity of ibrutinib.

Ibrutiniband BTK inhibition in models of autoimmune disease

The primary interest during early development of ibrutinib was in autoimmune disease, especially in rheumatoid arthritis (RA). Pan et al. reported that the ibrutinib-related Celera compound 4 significantly inhibited arthritis development in a dose dependent manner, with up to >95% inhibition of disease development in a murine RA model induced by anticollagen antibodies and LPS[38]. Honigberg et al. reported that ibrutinib inhibited collagen-induced arthritis (CIA), as well as autoantibody production and development of kidney disease in the MRL-Fas(lpr) lupus model[10]. Along the same lines, BTK blockade with a different inhibitor (CGI1746) inhibited BCR-dependent B cell proliferation and to reduced autoantibody levels in CIA [12]. Moreover, in this mouse model, BTK inhibition diminished FcγRIII-induced production of pro-inflammatory cytokines (TNFα, IL-1β, IL-6)[12], suggesting multiple targets of BTK inhibition in RA. Chang et al. tested ibrutinib in a series of arthritis and immune-complex (IC) animal models including CIA, collagen antibody-induced arthritis (CAIA), reversed passive anaphylactic reaction (RPA), and passive cutaneous anaphylaxis (PCA). The authors reported about high efficacy of ibrutinib in in CIA and in IC models that do not depend upon autoantibody production, indicating again that ibrutinib targets not only B cells but also other pro-inflammatory cells, such as monocytes, macrophages, and mast cells[11]. The complex role of BTK in autoimmunity is further highlighted in an elegant mouse model reported by Kubo et al., demonstrating a link between augmented TLR9-induced BTK activation in PIR-B-deficient B-1 cells, causing excessive autoantibody production and autoimmunity[48]. Kil et al. reported about a mouse model in which Btk was overexpressed in B cells, resulting in spontaneous formation of germinal centers, increased numbers of plasma cell, antinuclear autoantibody production and systemic lupus erythematosus (SLE)-like autoimmune disease affecting kidneys, lungs, and salivary glands. These pathologic changes were absent in Btk transgenic mice overexpressing a kinase-inactive Btk mutant, and ibrutinib decreased germinal center B cells and plasma

cells and normalized B cell activation and differentiation[49]. Finally, in lupus-prone B6.Sle1 and B6.Sle1.Sle3 mice, ibrutinib dampens humoral and cellular autoimmunity, as well as lupus nephritis[50]. BTK also plays a role in bone metabolism by transmitting signals in osteoclasts downstream of RANK and ITAM. Mice lacking Btk and Tec show severe osteopetrosis caused by a defect in bone resorption[51]. These findings may be relevant not only in the context of arthritis, but potentially also in multiple myeloma.

Ibrutinib side effects and resistance

Based on the early-stage CLL and MCL trials, which at this time have the largest numbers of ibrutinib-treated patients, ibrutinib is very well tolerated, and the most common side effects were mild diarrhea, nausea, fatigue, upper respiratory tract infections, nausea, rash, dyspnea, and edema, all grade 1 and 2, typically self-limited and not requiring any therapeutic intervention[46,47]. Treatment delays or discontinuation due to side effects of ibrutinib are infrequent. Grade 3 and 4 toxicities in the CLL and MCL trials were mostly infectious complications, such as pneumonias, which are likely not treatment-related, but rather due to the disease-inherent immunosuppression, or cytopenias[46,47]. Unlike conventional chemo-immunotherapy, ibrutinib usually does not cause myelosuppression; in fact, most patients with anemia, thrombocytopenia, or neutropenia at initiation of ibrutinib therapy have major improvements in their normal hematopoiesis[46,52,53]. Effects of ibrutinib on platelet function has been discussed as a potential off-target effect, based on preclinical studies suggesting that BTK may play a role in platelet aggregation[54] by transmitting signals from platelet membrane glycoprotein (GP) Ib. Quek et al. reported that Btk is important for signaling via the collagen receptor glycoprotein VI (GPVI) in platelets[55]. The findings of these *in vitro* study, however, need to be interpreted with caution, as emphasized by Jackson et al.[56], and XLA patients, which have defective BTK, do not have an increased risk for bleeding events[9]. At the 2012 ASH meeting, Farooqui et al. presented data about platelet numbers and function in 25 patients treated with ibrutinib. Their analysis indicates that ibrutinib does not have any significant effects on platelet function, and platelet counts improved rapidly in the majority of patients[52].

Data about the frequency of relapses and/or disease progression on therapy with ibrutinib are at this time very premature, but in CLL the frequency of such events appears to be low, with an estimated PFS of 96% at 26 months follow-up in previously untreated CLL patients, and a PFS of 75% at 26 months follow-up in relapsed/refractory CLL patients[46]. Potential mechanisms of primary or acquired resistance to ibrutinib are currently unknown and likely will become an area of research within the next few years, once ibrutinib is more widely used.

Conclusions

Inhibition of BCR signaling with the BTK inhibitor ibrutinib is emerging as a highly active new targeted therapy for patients with selected B cell malignancies, with the majority of data currently in patients with CLL and MCL, but results are promising in other NHL subtypes including FL and DLBCL of the ABC sybtype. Ibrutinib functions as an irreversible BTK inhibitor by bonding to Cys-481 in the ATP binding domain of BTK, it is orally bioavailable, well tolerated, and displays promising early activity in oftentimes heavily pre-treated patients[15]. Clinical responses are characterized by an early resolution of enlarged lymph nodes and organs (i.e. spleen), which is accompanied by “mobilization” of tissue-resident lymphoma cells into the blood (in CLL and MCL patients) during the first few months of therapy. Moving forward, we need to closely monitor durability of responses, risk for disease transformation and drug resistance, and long-term side effects. Another important, yet unanswered question is the value of combinations of ibrutinib with conventional cytotoxic or immunotherapy. Time to maximum response with reduction of circulating lymphocytes with single-agent therapy with ibrutinib takes relatively long and the early lymphocytosis, although clinically generally not significant, may be felt distracting. Therefore, combinations with B cell-targeted antibodies, such as rituximab[53], are a logical extension of the single-agent experience with ibrutinib. Combinations with cytotoxic drugs likely will accelerate time to remission and increase depths of remissions, but also likely at the expense of higher toxicity. Both single agent and combination trials with ibrutinib are ongoing (see Table 1), and more mature data from these trials will provide us with guidance towards the optimal use of ibrutinib in CLL, MCL, and other B cell malignancies.

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Potential conflict of interest:

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FIGURE LEGENDS

Figure 1

BTK signaling pathways. BTK is involved in the signaling of multiple receptors that together control cell migration, adhesion, survival and proliferation. Activation of BTK is triggered upon BCR stimulation, for example after antigen (Ag) binding, as shown on the left hand side. The BCR signaling pathway is thought to play a major role in mediating B cell survival and proliferation in normal and neoplastic B cells[19,24]. In addition, BTK mediates signals derived from chemokine receptors, such as the CXCR4 receptor [4,14], which binds to the chemokine CXCL12 (SDF-1) to mediate homing and migration. Both CXCR4 and the BCR also regulate adhesion molecules such as integrins[2] which are essential for tissue homing and retention. Consequently, inhibition of BTK results in re-distribution of tissue-resident CLL cells into the blood and inhibition of re-homing[43]. Abbreviations: PIP2, Phosphatidylinositol 4,5-bisphosphate; DAG, diacylglycerol; Ca^{++}, calcium.

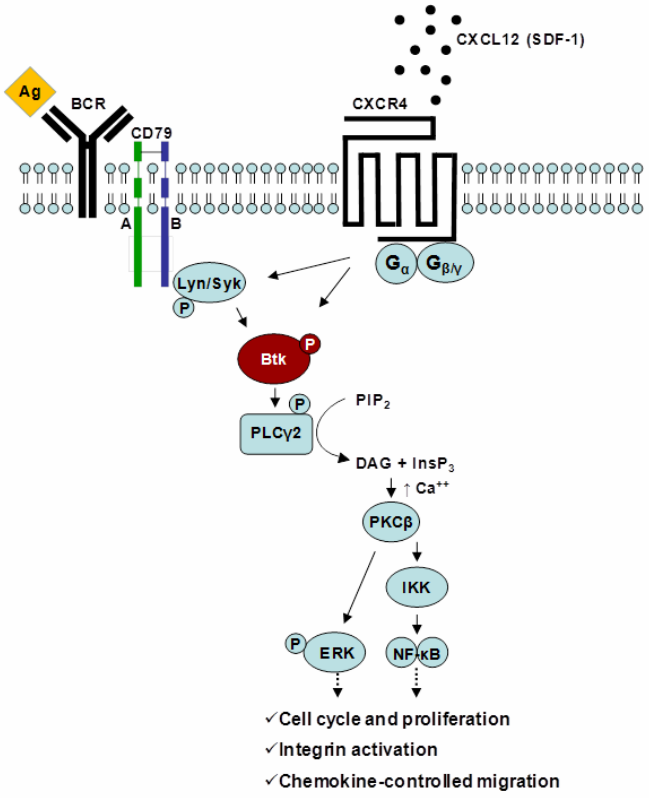

Figure 2

Chemical structure of the irreversible BTK inhibitor ibrutinib (PCI-32765).

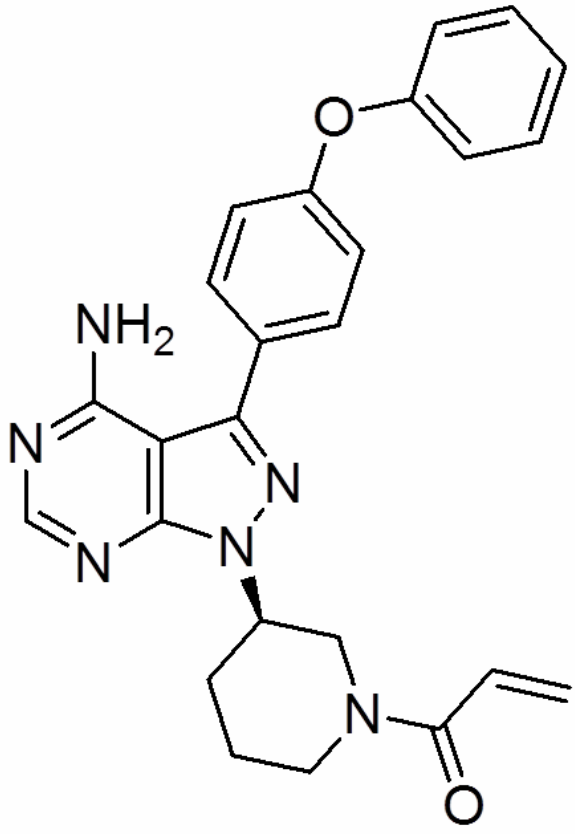

Figure 3

Proposed binding mode of ibrutinib in a homology model of BTK. The highlighted residue in the center is the covalently bound Cys481.

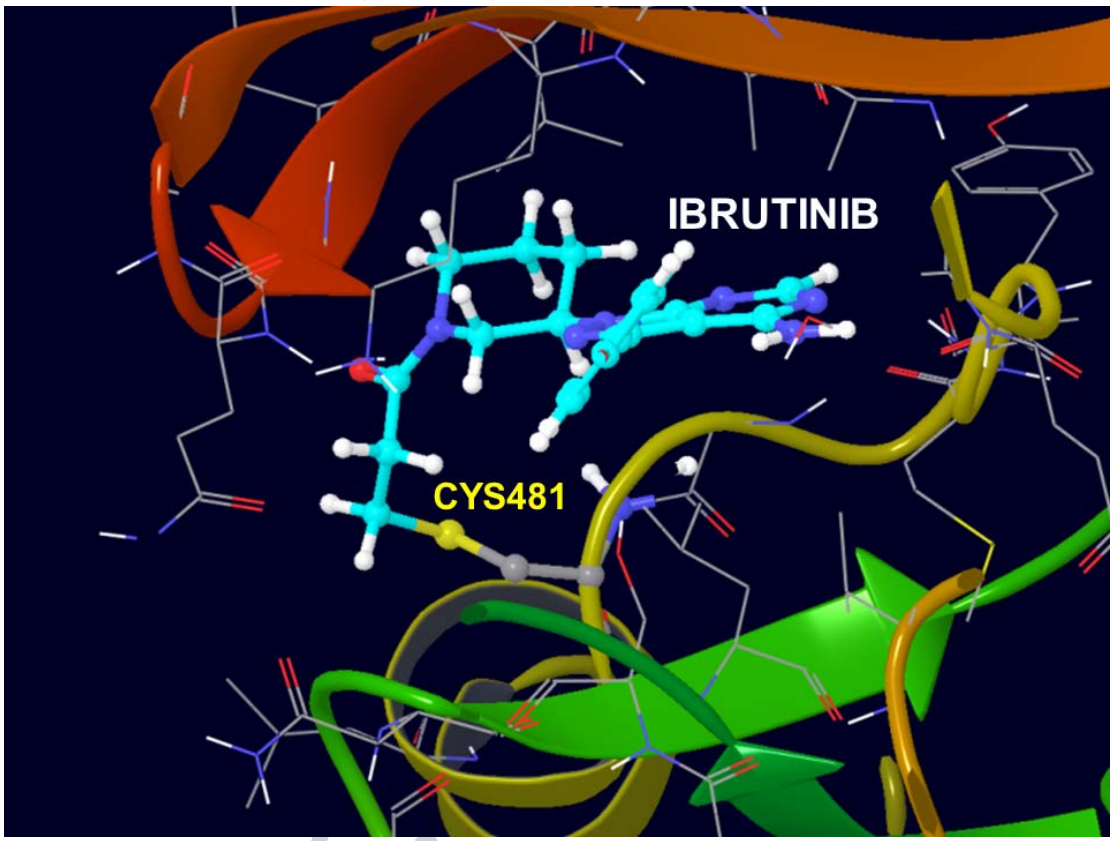

TABLE LEGEND

Table 1

Selected ongoing clinical trials of ibrutinib in B cell malignancies.

Study Title	Study Phase	Primary Objectives	Secondary Objectives	Estimated Enrollment	Clinical Trials.gov Identifier	Status
Ibrutinib Versus Ofatumumab in Relapsed or Refractory CLL (RESONATE™)	3	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-naive CLL or SLL (RESONATE™-2)	3	PFS	ORR, MRD negative CR, safety	272	NCT01722487	Enrolment start 01/2013, estimated completion in 02/2016
PCI-32765 (Ibrutinib) in Treating Patients With Relapsed or Refractory CLL, SLL, or B-cell PLL	2	2 year PFS	ORR, duration of response (DOR), OS	75	NCT01589302	Recruiting, estimated completion in 12/2014
Effects of PCI-32765 on Leukemia Cell Kinetics and Trafficking, Using Heavy Water Labeling in Subjects With CLL and SLL	Pilot	Impact of PCI-32765 on Leukemia Cell Trafficking and Death		30	NCT01752426	Recruiting, estimated completion in 12/2015
Multicenter Phase 2 Study of PCI-32765 (Ibrutinib) in Patients With Relapsed or Refractory CLL or SLL With 17p Deletion (RESONATE™-17)	2	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)	3	PFS	ORR, OS, side effects	580	NCT01611090	Recruiting, estimated completion in 08/2015
Safety and Tolerability Study of PCI-32765 Combined With FCR and BR in CLL	1/2	prolonged hematologic toxicity	adverse events, ORR	60	NCT01292135	No longer recruiting, estimated completion in 03/2013
Study of the Bruton's Tyrosine Kinase Inhibitor in Subjects With Relapsed or Relapsed and Refractory Multiple Myeloma	2	Efficacy as defined by clinical benefit rate	ORR, PFS, safety and tolerability, Duration of Clinical Benefit Response (DCB)	164	NCT01478581	Recruiting, estimated completion in 07/2016
Ibrutinib Versus Temsirolimus in Patients With Relapsed or Refractory MCL Who Received at Least One Prior Therapy	3	PFS	ORR, OS, duration of response, Time-to-next treatment, safety	Phase 280	NCT01646021	Recruiting, estimated completion in 08/2014

Efficacy and Safety of Ibrutinib, in Patients With MCLWho Progress After Bortezomib Therapy	2	ORR	PFS, OS	110	NCT01599949	Recruiting, estimated completion in 09/2013
Rituxan/Bendamustine/PCI-32765 in Relapsed DLBCL, MCL, or Indolent Non-Hodgkin's Lymphoma	1	Maximum tolerated dose (MTD)	adverse events, ORR	48	NCT01479842	Recruiting, estimated completion in 10/2013

Table 2

Quick profile of ibrutinib. Abbreviations: MoA: Mechanism of action; MoR: Mechanism of resistance; MTD: Maximum tolerated dose; DLT: Dose limiting toxicity.

Drug name	Ibrutinib
Company	Pharmacyclics, Inc, Sunnyvale, California, USA
Other names	PCI-32765
MoA	BTK inhibitor, inhibits BCR signaling and tissue homing mechanism
MoR	Not known
MTD	MTD not reached in the Phase 1 study[15]
DLT	Two cases of DLT (hypersensitivity, neutropenia) in the Phase 1 study[15]
Schedule	420 MG PO daily
Any other unique feature	Irreversible BTK inhibitor, binds to Cys-481 in the kinase domain