Leukemia & Lymphoma, 2013; Early Online: 1–7
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ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2013.803226

informa
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REVIEW

Ibrutinib in chronic lymphocytic leukemia and B cell malignancies

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Abstract

Recent clinical data suggest remarkable activity of ibrutinib, the first-in-class covalent inhibitor of Bruton's tyrosine kinase (BTK), in chronic lymphocytic leukemia (CLL), as well as excellent activity in other B cell malignancies, including in particular mantle cell lymphoma and Waldenstrom macroglobulinemia. This review evaluates the data from ongoing clinical and correlative studies of ibrutinib in B cell malignancies with a particular focus on CLL, and considers these data in the context of other B cell receptor pathway inhibitors.

Keywords: Ibrutinib, BTK, CLL, NHL

Introduction

Bruton's tyrosine kinase (BTK) is a member of the Tec family of kinases that signals downstream of the B cell receptor (BCR). Loss of gene function in humans results in the disease X-linked agammaglobulinemia, indicating that BTK is required for B cell development and immunoglobulin production in humans. Ibrutinib is a first-in-class covalent inhibitor of BTK which binds at cysteine 481 with 50% inhibitory concentration (IC_{50}) 0.5 nM, resulting in inhibition of kinase activity that is more durable than the half-life of the drug and allows for daily dosing. Early preclinical work found that 10 nM was sufficient to completely and irreversibly occupy the active site of BTK [1]. Given its potency and this strong rationale, ibrutinib was tested in spontaneous dog lymphomas, and three of eight dogs had partial responses [1].

Several subsequent studies looking at the effects of ibrutinib *in vitro* in chronic lymphocytic leukemia (CLL) established that apoptosis can be induced, but modestly and at high drug concentrations, while tritiated thymidine incorporation can be blocked at lower drug concentrations [2]. In addition and perhaps more importantly, ibrutinib certainly modulates the interaction between CLL cells and the microenvironment. It blocks signaling and activation through the BCR and CD40L, and can block the supportive effects of stromal cell co-incubation [2,3]. Ibrutinib also inhibits integrin-mediated adhesion to fibronectin and inhibits signaling and adhesion in response to CXCL12 and CXCL13 [3,4]. In an adoptive transfer model of the TCL1 mouse, ibrutinib potently reduced tumor progression, while also causing an early lymphocytosis similar to what is seen in humans [4].

The phase 1 study of ibrutinib in hematologic malignancies enrolled patients with any B cell lymphoma including CLL into five cohorts of punctuated dosing (28 days on, 7 days off) and two cohorts of continuous dosing [5] (Table I). Fifty-six patients were enrolled with a median of three prior regimens. Ibrutinib was well tolerated with only two dose limiting toxicities, a grade 3 allergic hypersensitivity in a patient with a history of similar reactions, and a dose interruption of more than 7 days for grade 2 neutropenia which resolved [5]. Pharmacokinetic studies found an initial mean half-life of 2–3 h with a terminal half-life of 4–8 h. Pharmacodynamic studies using a competitive binding assay established at least 95% BTK occupancy at doses of 2.5 mg/kg and above. A dose of 560 mg daily was recommended for further study [5]. The overall response rate on this study was 60% with 16% complete remissions (CRs), with the following results by histology: CLL, 11 of 16 with two CRs, 69%; mantle cell lymphoma (MCL), seven of nine with three CRs, 78%; follicular lymphoma, six of 16 with three CRs, 38%; Waldenstrom macroglobulinemia (WM), three of four, 75%; and diffuse large B-cell lymphoma (DLBCL), two of seven, 29%. Median progression-free survival (PFS) was 13.6 months for all patients [5]. The response pattern noted in the patients with CLL was similar to what has been described with other kinase inhibitors that affect the B cell receptor pathway, namely a rapid reduction in lymphadenopathy with early increase in lymphocytosis [6–8]. The lymphocytosis stabilizes in the first couple of months, but the degree and rapidity with which it improves over time varies with the specific drug and the patient population.

Ibrutinib in non-Hodgkin lymphomas

The results of the phase 1 study suggest broad activity for ibrutinib in B cell lymphomas, and updated results were

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Received 13 March 2013; revised 24 April 2013; accepted 3 May 2013

reported at the 2012 meeting of the American Society of Hematology (ASH) (Table I). An update on the 16 patients with follicular lymphoma from the original phase 1 study was presented [9]. The median age of these 16 patients was 60, and they had had a median of three prior regimens. Follicular lymphoma international prognostic index (FLIPI) scores were high in 44% and intermediate in 38%. Eleven evaluable patients treated at doses of at least 2.5 mg/kg/day, resulting in full BTK occupancy, showed an overall response rate (ORR) of 55% with 27% CRs and median PFS 13.4 months. The nine patients treated at doses of at least 5 mg/kg had a median PFS of 19.6 months, with two patients remaining on study at 25 and 29 months. These results suggest that ibrutinib has significant activity in follicular lymphoma, and is certainly worthy of additional study. An ongoing phase 2 potential registration trial is assessing the efficacy of ibrutinib in patients with follicular lymphoma who have received at least two prior regimens and who were most recently treated with an anti-CD20 antibody in combination with chemotherapy, and showed no response or relapse within 12 months of that prior regimen.

Phase 2 data in mantle cell lymphoma were also presented at ASH (Table I). Similar to CLL, MCL had a very high response rate in the phase 1 study in a limited number of patients. A multicenter phase 2 study of single agent ibrutinib at 560 mg daily was therefore initiated in MCL and interim results were presented at ASH 2012 [10]. One hundred and fifteen patients were enrolled, 65 bortezomib-naive and 50 previously treated with bortezomib. The median age was 68 and the median number of prior regimens was three. Some 44% had disease refractory to their most recent prior regimen. The ORR was 62% with 20% CRs, with a median time on study of 9.2 months; no apparent difference in response was seen based on prior bortezomib exposure. Longer-term follow-up of the first 51 patients reported a year earlier, now at a median of 15 months' follow-up, suggested improving responses, with a 75% ORR and 39% CRs. The median PFS was 13.9 months for all treated patients [10]. Based on these data a pivotal registration trial has been initiated in patients with relapsed/refractory MCL previously exposed to bortezomib.

Ibrutinib in diffuse large B-cell lymphoma

In DLBCL, interim results of a multicenter phase 2 study assessing response within the two major biologic subgroups of DLBCL, namely activated B cell (ABC) or germinal center B cell (GCB), were presented (Table I). The ABC subtype is associated with significantly worse overall survival than the GCB subtype with standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy [11]. The rationale for this subdivision in the study is the known constitutive activation of B cell receptor signaling in ABC type DLBCL [12], which depends on this activation for survival, suggesting that ibrutinib would have particular activity in this group. In addition, this dependence is driven in at least some cases by somatic mutations affecting the B cell receptor (BCR) and nuclear factor-κB (NFκB) pathways. For example, CD79A/B mutations, which are upstream of BTK in the BCR pathway and drive activation of the pathway, are seen in 21% of ABC subtype DLBCL, while CARD11 mutations, which are downstream of BTK and also pathway-activating, are seen in 10% [12,13]. Activating mutations of MYD88, which is in the Toll-like receptor pathway but converges with the BCR pathway to activate NFκB, are seen in 39% of ABC subtype DLBCLs [14].

Interim results of a multicenter phase 2 study of ibrutinib 560 mg daily in DLBCL were presented at ASH 2012 [15]. Seventy patients with median age 64 and a median of three prior regimens were enrolled. Some 23% had had a prior stem cell transplant and 54% had refractory disease. The primary endpoint was ORR in ABC and GCB subtypes. In the entire study population the ORR was 23% with 9% CRs, but the ORR in the 29 ABC type patients was 41%, while only one of 20 GCB type patients responded. A possible trend toward better OS in the ABC group (9.76 months [95% confidence interval (CI) 3.88–not reached (NR)]) compared to the GCB group (3.35 months [95% CI 1.22–NR]) was observed ($p = 0.099$). Of interest were preliminary data on the difference in response based on somatic mutations [15]. Five of seven patients with CD79B mutations responded, although 34% of those without CD79B mutations also responded,

Table I. Clinical results of ibrutinib reported to date*.

Disease	Study and patient population	ORR	CR	PFS
CLL	Phase 1 rel/ref [5]	11/16 (69%)	2/16 (12.5%)	NA
	Phase 2 rel/ref [22]	60/85 (71%)	2/85 (2%)	75% at 26 months
	Phase 2 elderly treatment-naive [22]	21/31 (68%)	3/31 (10%)	96% at 26 months
MCL	Phase 1 rel/ref [5]	7/9 (78%)	3/9 (33%)	NA
	Phase 2 rel/ref [10]	68/110 (62%)	22/110 (20%)	13.9 months
FL	Phase 1 rel/ref [5]	6/16 (38%)	3/16 (19%)	NA
	Update phase 1 rel/ref [9]; patients treated at ≥ 2.5 mg/kg/day	6/11 (55%)	3/11 (27%)	13.4 months
DLBCL	Phase 1 rel/ref [5]	2/7 (29%)	0/7 (0%)	NA
	Phase 2 [15]	23%	9%	NA
	Phase 2 GCB [15]	1/20 (5%)	NA	OS 3.35 months (1.22–NR)
	Phase 2 ABC [15]	12/29 (41%)	NA	OS 9.76 months (3.88–NR)
WM	Phase 1 rel/ref [5]	3/4 (75%)	0/4 (0%)	NA

CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; WM, Waldenstrom macroglobulinemia; rel/ref, relapsed refractory; GCB, germinal center origin; ABC, activated B cell origin; ORR, overall response rate; CR, complete remssion; PFS, progression-free survival; NA, not available because not reported; NR, not reached.

*Note on dosing: Patients enrolled on the phase 1 study received a range of doses. Phase 2 studies in NHLs were dosed at 560 mg daily while phase 2 studies in CLL were dosed at 420 mg or 840 mg daily. See text for further details.

suggesting alternative mechanisms of BCR pathway dependence. As one would predict, DLBCLs with CARD11 ($n = 4$) or MYD88 ($n = 5$) mutations appeared to be resistant to ibrutinib, with the caveat of very small numbers. DLBCLs with both CD79B and MYD88 mutations did respond ($n = 4$ of 5), however, suggesting perhaps that CD79B-driven BCR pathway activation was dominant compared to the Toll-like receptor pathway. The interim data from this study strongly support ABC subtype as a biomarker for response to ibrutinib, but any more detailed patient selection based on particular somatic mutations will certainly require much larger numbers of patients in order to draw firm conclusions. Future studies should consider targeting the ABC subtype and assessing differential responsiveness based on particular somatic mutations.

Ibrutinib as a single agent in chronic lymphocytic leukemia

Interestingly, despite the profound activity of ibrutinib in CLL, and in contrast to DLBCL, we have limited evidence for substantial genetic activation of the BCR pathway in CLL. The same MYD88 mutations seen in DLBCL are found probably at a somewhat lower frequency than initially reported in CLL, likely only 2–4% [16–19], and we have recently reported on somatic mutations throughout the NFκB pathway without a dominant driver apart from MYD88. Most of these mutations are not directly in the BCR signaling pathway [20]. These results suggest that pathway activation may often occur through other means, most likely sustained B cell receptor stimulation from the microenvironment [21]. This nearly universal support of CLL cells from the microenvironment may potentially explain what seems like close to universal activity of ibrutinib in CLL.

Several phase 2 ibrutinib monotherapy trials enrolled 116 patients with CLL between May 2010 and July 2011. These data were updated at ASH in December 2012 and have generated considerable excitement [22] (Table I). The patients were enrolled in three cohorts: (1) 31 treatment-naive patients 65 years or older, with median follow-up 20.3 months; (2) 61 patients with relapsed/refractory CLL, with median follow-up 22.1 months; and (3) 24 patients with high risk relapsed/refractory CLL, defined as no response or relapse within 24 months of initiation of a chemoimmunotherapy regimen, with median follow-up 14.7 months in that cohort. Approximately half of cohort 2 was treated with ibrutinib at 840 mg per day rather than the 420 mg of the other cohorts, and no evidence was found for improved response at the higher dose [22].

The treatment-naive cohort had a median age of 71. Some 48% had advanced Rai III/IV disease and 55% had unmutated *IGHV*; 7% had high-risk deletion 17p and 3% deletion 11q. These patients would have to be considered relatively low risk compared to patients enrolling on many other upfront studies designed for patients who meet criteria for needing therapy. For example, the German CLL Study Group CLL8 trial enrolled 63% of patients with unmutated *IGHV* and 33% with deletions 17p and 11q [23]. Nonetheless, the ibrutinib results are still quite impressive for a well-tolerated single agent. Altogether 84% of patients remain on therapy with a median time on treatment of 20.3 months. Diarrhea, nausea, fatigue and rash, mostly grade 1–2 and self-limited, remain the most common adverse events. Grade 3 infections have been seen in 10%, but hematologic toxicity has been minimal. The ORR is 68% with 10% CRs and an additional 13% partial responses (PRs) with lymphocytosis. The response category PR with lymphocytosis requires at least a 50% reduction in nodal disease in the setting of elevated lymphocyte count, and has been developed for BCR pathway inhibitory agents that cause a rapid decrease in lymphadenopathy along with an early increase in lymphocyte count. This phenomenon is thought to be due to the redistribution of CLL cells [24]. Patients in this category experience excellent clinical benefit similar to those with full partial responses, although the true duration of these responses is not yet known. However, in these previously untreated patients with CLL receiving ibrutinib, most of whom have partial responses, the 26-month PFS is 96% [22].

The data in relapsed/refractory CLL are also quite impressive. The two cohorts were pooled for presentation, and altogether 85 patients were enrolled, with a median age of 66 and a median of four prior regimens [22]. Some 65% had Rai III/IV disease, and 48% were deemed refractory, where refractory was taken as no response or progression within 12 months of a purine analog-containing regimen. In terms of their CLL biology, these patients were certainly high risk: 85% had unmutated *IGHV*, 35% deletion 17p and 39% deletion 11q. Median time on treatment was 15.7 months, with 64% of patients still on therapy. Eleven events of disease progression have occurred, seven of which were Richter transformation. Toxicity was greater than in the treatment-naive patients, with 40% of patients having a grade 3 or greater infection, including one death due to cryptococcal pneumonia. Grade 3–4 neutropenia also approached 20%. Nonetheless these toxicities are certainly no worse and in many cases better than what would be seen with other therapies in this patient population [22].

The efficacy in this subgroup is again very high: ORR was 71% with 2% CRs and an additional 18% PRs with lymphocytosis. Approximately 80% of patients with baseline anemia or thrombocytopenia experienced sustained improvement in these counts. Response rate did not differ by risk features, with deletion 17p patients having a 68% ORR. The PFS for all patients was estimated at 75% at 26 months. Notably, the PFS for patients without 17p or 11q deletions was 93%, while it was 73% for patients with 11q deletions and 57% for patients with 17p deletions. Although PFS for the latter two high risk groups is not as high as for the lower-risk patients, it is nonetheless remarkably good for pretreated patients with deletions 17p and 11q. In a recent study looking at 28 relapsed patients with 17p deletion treated with high dose dexamethasone and alemtuzumab, arguably our most active current therapy, the median PFS was 10.3 months [25]. Patient selection can certainly affect these outcomes, but the ibrutinib data are nonetheless quite good.

Ibrutinib combination studies in chronic lymphocytic leukemia

Early data have also been reported on ibrutinib in combination with bendamustine and rituximab (BR), with fludarabine cyclophosphamide and rituximab (FCR), with ofatumumab, with rituximab. The most recent update of the phase 1b combination study with BR/FCR was presented at the European Hematology Association (EHA) last year [26]. Ibrutinib at 420 mg daily was combined with up to six cycles of standard dose BR or FCR in parallel cohorts in relapsed CLL. The BR cohort enrolled 30 patients with a median age of 62 and a median of two prior therapies. Some 47% had Rai III–IV disease, and 37% were refractory to purine analogs, where again this was defined as progression within 12 months of their most recent prior chemoimmunotherapy. Deletion 17p was seen in 23% and deletion 11q in 43%. The therapy was well tolerated, with bendamustine dose reductions required in 23% of patients and only 17% and 10% of patients having grade 3 or 4 hematologic toxicity, respectively. Serious adverse events included one case of tumor lysis syndrome, two cases of grade 3 cellulitis and one case of febrile neutropenia. Lymphocytosis was largely abrogated with the addition of BR, so the ORR was 93% with 13% CRs at a median follow-up of 8.1 months [26]. Not all patients had been evaluated with bone marrow biopsy to establish CR, and patients are continuing on ibrutinib indefinitely, so the CR rate may increase with time. The estimated 11-month PFS is 90%. These data compare favorably to those previously published by Fischer *et al*. for the BR regimen alone, in which the response rate was 59% and CR rate 9% [27].

Eligibility for the FCR cohort required that patients be previously treated yet purine analog-naive, and good candidates for FCR [26]. These criteria substantially limited enrollment and the cohort closed early after three patients were treated, all at Dana-Farber Cancer Institute (DFCI). All three patients completed six cycles and the therapy was well tolerated. All three patients responded, two with complete remissions, and continue on ibrutinib monotherapy.

Early combination data for ibrutinib with ofatumumab and ibrutinib with rituximab have also been presented. The Ohio State group is conducting a phase 1b/2 study exploring three different dosing schedules of ibrutinib with ofatumumab, and reported on one of them at the American Society of Clinical Oncology (ASCO) 2012 meeting, specifically initiation of ibrutinib 4 weeks prior to ofatumumab, starting with cycle 2 [28]. Twenty-seven patients had been enrolled, with median age 66 and a median of three prior regimens. Some 48% had advanced Rai stage III–IV disease and 41% were refractory to purine analogs. Altogether 91% had unmutated *IGHV*, 37% 17p deletion and 33% 11q deletion, so again it was a high-risk population. The ORR was 100% with one CR (4%). Two of three enrolled patients with Richter syndrome responded, with one in ongoing response at 10.1 months. Eighty-nine percent of patients remained on study with a median follow-up of 9.8 months. In addition to the usual mild adverse events of ibrutinib, neuropathy was seen in 25% of patients, but was likely more related to ofatumumab, given the absence of neuropathy in other ibrutinib studies and recent reports of neuropathy with ofatumumab [29].

The ibrutinib–rituximab study is from M. D. Anderson and was just presented at ASH 2012 [30]. Forty patients with either 17p deletion or p53 mutation (upfront or relapsed), or relapsed either with 11q deletion or within 3 years of a frontline chemoimmunotherapy regimen, were enrolled. They received rituximab 375 mg/m^2 weekly for four doses and then monthly for 6 months. Ibrutinib was continued daily at 420 mg for at least 12 months. The median age was 65, and the patients had had a median of two prior regimens. Some 73% had Rai III–IV disease, 80% had unmutated *IGHV*, 50% deletion 17p and 33% deletion 11q. This patient population is definitely high risk, yet still showed ORR 83% at 3–6 months for all 40 patients, with one CR (3%). Only two patients have been removed from study therapy thus far. The data were not yet mature enough to present PFS data, but certainly look encouraging. An interesting question in this case is whether and how much rituximab is adding to single-agent ibrutinib. A planned upcoming randomized US cooperative group trial intends to address this question in the upfront therapy of the elderly, with treatment arms that will include ibrutinib alone, ibrutinib with rituximab, and bendamustine with rituximab.

Ibrutinib and platelet function

Throughout the ibrutinib studies, ecchymosis has been seen at varying rates, ranging up to almost half the patients on the Ohio State ibrutinib–ofatumumab study [28]. This bruising may reflect the fact that BTK is expressed in platelets and involved in their activation by collagen and shear stress [31,32]. Platelets from patients with Bruton's X-linked agammaglobulinemia are also hyporesponsive to collagen, suggesting that loss of BTK does have a direct effect on platelet function. The clinical significance of this remains unclear, although as noted, some patients on ibrutinib complain of easy bruisability and delayed wound healing. Several intracranial hemorrhages have occurred on ibrutinib studies, albeit in the setting of head trauma and therapeutic anticoagulation, particularly with warfarin [10]. At ASH 2012, Farooqui *et al*. reported preliminary data from platelet aggregation studies done during their ongoing single agent ibrutinib trial, and found largely normal platelet aggregation in response to adenosine diphosphate (ADP) and epinephrine [33], but did not test collagen or shear stress. These findings are reassuring, but nonetheless, ongoing ibrutinib studies recommend holding ibrutinib for 7 days prior to and after invasive procedures, and avoiding its co-administration with warfarin anticoagulation in particular. More extensive clinical experience will be required to truly define the degree, if any, of this risk.

Correlative studies of ibrutinib *in vivo* in humans

Recent data again from ASH 2012 are starting to provide some insights into the mechanism of action of ibrutinib

in vivo. Herman *et al*. from Adrian Wiestner's group at the National Heart, Lung, and Blood Institute (NHLBI) reported that, following initiation of single agent ibrutinib, CLL cells show a reduction in the activation markers CD38, CD69 and CD86, along with a marked reduction in Ki67 in both peripheral blood and lymph nodes, reflecting a reduction in proliferation [34]. Similar Ki67 results in peripheral blood were also reported from Cornell [35]. On the NHLBI study, gene expression profiling data from both peripheral blood and lymph node CLL cells showed the expected decrease in BCR signaling and NFκB activation in patients receiving ibrutinib [34]. In Jan Burger's ongoing clinical trial of ibrutinib and rituximab, secretion of CCL3 and CCL4 is nearly ablated, again consistent with reduced signaling through the BCR [30]. These findings suggest that ibrutinib reduces both activation and proliferation of CLL cells through an on-target mechanism. Although apoptosis is difficult to detect *in vivo*, the improvement in tumor burden seen in these patients suggests that it is occurring [36].

These observations that ibrutinib inhibits BCR signaling have suggested that its efficacy may be greatest in CLLs with enhanced BCR signaling, namely those with unmutated *IGHV* or positive for ZAP70. The clinical data show an equivalent PFS for the higher risk patients with unmutated *IGHV* [22], and make an interesting observation regarding lymphocytosis. Specifically, persistent increased lymphocytosis in the phase 2 CLL data occurred in 50% of patients with mutated *IGHV* as compared to 15% of unmutated ($p = 0.025$), and the median time to normalization was 6.4 months for unmutated compared to 14.8 months for mutated ($p = 0.068$). Although the etiology of this observation is presently unclear, possible explanations could include that unmutated CLLs with more active BCR signaling are more sensitive to the apoptosis-inducing effects of ibrutinib, or that they are more primed to undergo apoptosis following the withdrawal of survival signals, i.e. more dependent on the microenvironment, as has been suggested by our group and others [37,38].

Questions have been raised about why ibrutinib induces a relatively low CR rate in the setting of excellent PFS. The early data described above suggest some possible contributing factors. For example, if ibrutinib works primarily through modulation of microenvironmental support and inhibition of proliferation rather than induction of cytotoxicity, these mechanisms may clear tumor relatively slowly and/or make clearance of the last residual CLL cells harder. The evidence above also suggests that ibrutinib makes the cells more quiescent, which likely keeps them from proliferating or expanding, but could conceivably also make them harder to kill. Further work clarifying the *in vivo* mechanism of action of ibrutinib will likely shed light on this question.

Ibrutinib in context of other B cell receptor pathway inhibitors

The accumulated data for ibrutinib in CLL are impressive, and are currently at the forefront of the BCR pathway inhibitors. Many other drugs have been tested or are currently in clinical development, however, and some comparison among them is instructive. Data are summarized in Table II. The response pattern of nodal decrease with redistribution lymphocytosis is clearly a class effect of these drugs, but one which nonetheless shows significant variability in the frequency of objective nodal response, degree and persistence of lymphocytosis, and response rate and PFS by classic criteria (Table II). Patients on these drugs can develop a marked lymphocytosis with stable or minor nodal response, while conversely, some patients have a nodal response without lymphocytosis. Thus, while lymphocytosis is a clear pharmacodynamic effect, it does not always correlate with deep clinical and nodal response, suggesting that redistribution and clinical response may result from inhibition of different but possibly overlapping sets of signaling pathways. For example, dasatinib, everolimus and fostamatinib all show redistribution without markedly high nodal response rates [7,8,39]. Idelalisib, the delta-specific phosphatidylinositol 3-kinase (PI3K) inhibitor formerly known as CAL101 and GS1101, has shown much higher nodal response rates, with frequent lymphocytosis whose persistence has limited the overall response rate, despite many patients deriving prolonged long-term benefit [6,40]. Response rates by classic criteria are higher with ibrutinib due to resolution of lymphocytosis, allowing more formal partial responses [22]. Although the data with ibrutinib appear better than the data with idelalisib, an element of caution against overinterpretation is in order, since ibrutinib has phase 2 data while idelalisib has only phase 1 data, and the idelalisib patients were more heavily pretreated [22,40].

Many other BCR pathway inhibitors are also in various stages of clinical development for CLL, including pan- and other delta-specific PI3K inhibitors. At present it is too early to know if greater clinical activity is primarily target-related, drug-related or both. Included in Table II are IPI-145 and

Table II. Clinical activity of selected BCR pathway inhibitors in relapsed refractory CLL.

Target	Drug	Nodal response rate	Lymphocytosis rate	Overall response rate	PFS
LYN (?BTK)	Dasatinib [39]	47% (7/15)	Not reported	20% (3/15)	TTF 6.7 months
SYK	Fostamatinib [7]	55% (6/11)	69% (9/13)	Not reported	6.4 months
mTOR	Everolimus [8]	45% (10/22)	36% (8/22)	18% (4/22)	5.1 months
PI3Kδ	Delta-specific: idelalisib (GS1101) [40]*	83% (46/55)	58% (32/55)	24% (13/55)	15 months†
	Gamma, delta-specific: IPI-145 [41]*	82% (9/11)	64–73% (6–8/11)	55% (6/11)	Too early
BTK	Ibrutinib (PCI-32765) [22]	88% (75/85)	78% (63/81)	71% (58/85)	75% at 26 months
	CC-292 (AVL-292) [42]*	9% (1/11)	55% (6/11)	0% (0/11)	Too early

BCR, B cell receptor; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; LYN, Lck/yes-Related Novel Protein Tyrosine Kinase; mTOR, mammalian target of rapamycin; PFS, progression-free survival; PI3Kδ, Phosphatidylinositol 3-kinase-delta; SYK, spleen tyrosine kinase; TTF, time to treatment failure.
*Phase 1 study.
†PFS 15 months for all patients; 18 months for those treated at doses ≥ 150 mg BID (recommended phase 2 dose).

Table III. Advanced phase/registration trials of ibrutinib in B cell malignancies.

Disease	Trial name	Patient population	Treatment intervention	Primary endpoint
CLL	RESONATE, phase 3	Relapsed refractory unfit for purine analogs	Ibrutinib vs. ofatumumab	PFS
	RESONATE-17, phase 2	Relapsed 17p deletion	Ibrutinib	ORR
	RESONATE-2, phase 3	Untreated elderly	Ibrutinib vs. chlorambucil	PFS
	HELIOS, phase 3	Relapsed refractory at least one prior therapy	BR + ibrutinib vs. BR + placebo	PFS
	US intergroup, phase 3, alliance A041202	Untreated elderly	BR vs. ibrutinib vs. ibrutinib–rituximab (IR)	PFS
	US intergroup, phase 3, ECOG 1912	Untreated fit	FCR vs. IR	PFS
	UK NCRI CLL, phase 3, CLL10	Untreated fit	FCR vs. IR	PFS
MCL	SPARK, phase 2	Relapsed after bortezomib, received ≥ 1 prior rituximab-containing regimen	Ibrutinib	ORR at 6 months after last patient enrolls
	SHINE, phase3	Untreated elderly	BR + ibrutinib vs. BR + placebo	PFS
	RAY, phase 3	Relapsed refractory at least one prior therapy	Ibrutinib vs. temsirolimus	PFS
FL	Phase 2	Refractory ≥ 2 prior regimens and progressed within 12 months of last CD20 CIT	Ibrutinib	ORR
WM	Phase 2	Relapsed at least one prior regimen	Ibrutinib	ORR, major response, VGPR/CR

CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; FL, follicular lymphoma; WM, Waldenstrom macroglobulinemia; CIT, chemoimmunotherapy; BR, bendamustine and rituximab; FCR, fludarabine, cyclophosphamide and rituximab; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete remssion.

CC-292, although their data from ongoing phase 1 trials are still extremely early. Thus far, IPI-145 shows promising response rates similar to idelalisib and ibrutinib [41]. The low level of response with CC-292 at this point may reflect the low doses tested and few patients treated as of the date of the report [42], but may also reflect fundamental differences between CC-292 and ibrutinib. CC-292 [43] is a more specific BTK inhibitor than ibrutinib, which has the potential to covalently inhibit six other kinases and to potently but non-covalently inhibit another 11 kinases, with $IC_{50} < 100$ nM [1]. In fact, in the case of interleukin-2 inducible kinase (ILK), ibrutinib has recently been demonstrated to function as an irreversible inhibitor [44]. Thus, ibrutinib may inhibit other targets as well as BTK, which may influence its clinical activity. Future work will be required to define this, but for now, as Table II shows, ibrutinib has marked activity that puts it in the forefront of an emerging class of highly effective drugs for CLL and likely other B cell malignancies.

Summary

The impressive clinical data to date for ibrutinib across multiple B cell malignancies has led to an extensive program of registration trials, particularly in CLL and MCL, which are summarized in Table III. In addition, the Food and Drug Administration (FDA) has recently granted ibrutinib a Breakthrough Therapy Designation for mantle cell lymphoma, Waldenstrom macroglobulinemia and, most recently, CLL with 17p deletion, which may hasten its approval. The phase 2 data on ibrutinib in Waldenstrom macroglobulinemia that contributed to this decision are expected at ASCO 2013.

The future of ibrutinib in B cell malignancies appears bright. It seems likely that upon approval it will rapidly transform therapy for the elderly, for whom the single agent is likely to be a highly effective and well tolerated therapy. Studies are initiating which will determine whether adding an anti-CD20 antibody is beneficial, and how ibrutinib-based therapy compares to chemoimmunotherapy in adequately fit patients. Much scientific work remains to truly understand its mechanism of action in different diseases, and how the unusual pattern of lymphocytosis response relates to that mechanism of action. At present very little is known about mechanisms of resistance, and whether resistance may occur more frequently as Richter transformation in patients maintained on ibrutinib. Better understanding of these mechanisms will impact the design of the most rational combinations of ibrutinib with other novel agents, including perhaps other BCR pathway inhibitors, as well as antibodies or other classes of small molecules such as BCL-2 inhibitors. The next several years promise to be most interesting as our understanding of these mechanisms grows and we learn how best to use ibrutinib for the maximum benefit of our patients.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

J. R. B. is a Scholar in Clinical Research of the Leukemia and Lymphoma Society and is supported by grants from the Leukemia and Lymphoma Society and the American Cancer Society.

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