

Bruton tyrosine kinase inhibitors: a promising novel targeted treatment for B cell lymphomas

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Summary

Constitutive or aberrant signalling of the B cell receptor signalling cascade has been implicated in the propagation and maintenance of a variety of B cell malignancies. Small molecule inhibitors of Bruton tyrosine kinase (BTK), a protein early in this cascade and specifically expressed in B cells, have emerged as a new class of targeted agents. There are several BTK inhibitors, including ONO-WG-307, LFM-A13, dasatinib, CC-292, and PCI-32765 (ibrutinib), in preclinical and/or clinical development of which ibrutinib is currently in phase III trials. Recent clinical data suggest significant activity of ibrutinib as a first in class oral inhibitor of BTK. This review provides an overview of ongoing clinical studies of BTK inhibitors.

Keywords: Bruton tyrosine kinase, B cell receptor signalling, refractory non-Hodgkin lymphoma, ibrutinib, CC-292.

B cell receptor signalling pathway

The B cell receptor (BCR) signalling pathway plays a fundamental role in determining B cell fate and function by regulating cellular selection, maturation, proliferation, and antibody production (Fig 1) (Dal Porto *et al*, 2004). The receptor consists of a surface transmembrane immunoglobulin (Ig) associated with the Ig α (CD79A) and Ig β (CD79B) chains (Wiestner, 2012). In normal B cells, antigenic binding to the BCR results in receptor aggregation and subsequent phosphorylation of the receptor's cytoplasmic tyrosine-based activation motifs (ITAMs) by the recruited SRC-family kinases LYN and SYK (Wiestner, 2013). SYK propagates the signal through activation of phosphoinositide 3-kinase (PI3K δ), which in turn mediates the conversion of phosphatidylinositol 4,5 bisphosphate (PIP2) to phosphatidylinositol 3,4,5 triphosphate (PIP3) (Wiestner, 2013). The ensuing recruitment

of Bruton tyrosine kinase (BTK) further transmits and amplifies the signal via phosphorylation of phospholipase C gamma 2 (PLC γ 2), mobilization of calcium secondary messengers, and eventual activation of MAP kinase pathways, nuclear factor of activated T cells (NFAT), and nuclear factor κ B (NF κ B). These signals regulate patterns of gene expression necessary for B cell survival and proliferation (Brown, 2012; Wiestner, 2013).

While the BCR signalling cascade is generally antigen-dependent in normal B cells, antigen-independent signalling, also known as 'tonic' signalling, has been shown to exist (de Rooij *et al*, 2012). An overactive antigen-independent pathway is thought to be a contributing factor to B cell malignancies characterized by constitutively or aberrantly active BCR signalling (Monroe, 2006; Rinaldi *et al*, 2006; Chen *et al*, 2008; Davids & Brown, 2012; Dühren-von Minden *et al*, 2012). Specifically, overactive signalling promotes the development of a supportive tumour microenvironment by modulating chemokine-controlled migration and integrin-mediated adhesion, while lack of such support leads to rapid apoptosis in B cells (de Rooij *et al*, 2012; Wiestner, 2012). Consistent with this, several inhibitors of protein kinases involved in BCR signalling have achieved notable clinical results: a LYN inhibitor (Bafetinib), a SYK inhibitor (Fostamatinib), and a PI3K δ inhibitor (Idelalisib) (Robak & Robak, 2013).

Bruton tyrosine kinase as a unique target of inhibition

Among the many kinases involved in BCR signalling, BTK, a tyrosine kinase member of the Tec kinase family, is a unique therapeutic target. Loss of gene function mutations of *BTK* in humans results in X-linked agammaglobulinaemia (XLA), characterized by a complete lack of B cells, low levels of serum Ig, and recurring infections. This suggests that BTK is required for B cell development and immunoglobulin production (Maas & Hendriks, 2001). As with other kinases in the BCR pathway, inhibition of BTK has been shown to inhibit NF κ B DNA binding, reduce integrin-mediated cell adhesion and migration, limit cell production of chemokines, diminish cellular response to chemotactic factors, and ultimately induce apoptosis (Herman *et al*, 2011; Ponader *et al*, 2012; de Rooij *et al*, 2012).

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The druggability of BTK is supported by the clinical phenotype of patients with XLA, where a lack of functioning BTK is both nonlethal and selective to only B cells as opposed to T cells (Herman *et al*, 2011). This selectivity for B lymphocytes is promising as inhibitors of BTK will hypothetically take less of a toll on a patient's naturally occurring immune cells. These properties have made inhibition of BTK an attractive target in pharmacology with several drugs in the development pipeline. Published data are available for at

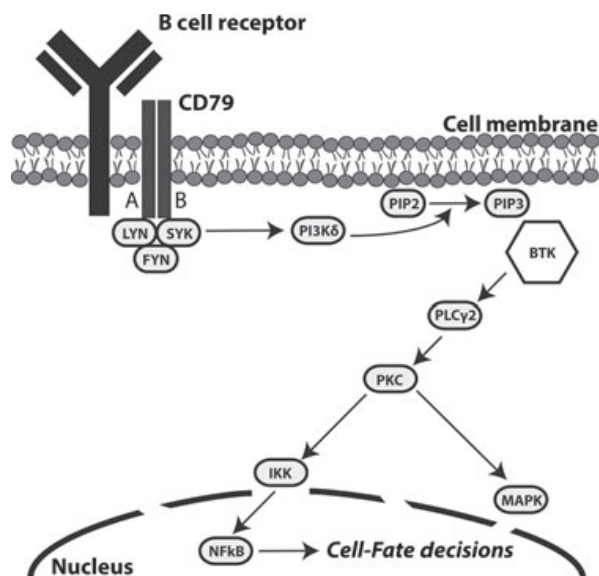


Fig 1. The BCR signalling cascade. Antigen binding to the B cell receptor initiates kinase-mediated signal transduction resulting in activation of secondary messengers and, ultimately, transcription factors that regulate cell fate.

least five BTK inhibitors that vary in specificity and mechanism of binding: ONO-WG-307, LFM-A13, dasatinib, CC-292, and ibrutinib (PCI-32765) (Table I).

ONO-WG-307 (ONO Pharmaceutical Co., Osaka, Japan)

ONO-WG-307 is an oral, potent (50% inhibitory concentration [IC₅₀] = 2 nmol/l), reversible inhibitor of BTK that acts by blocking auto-phosphorylation at the Tyr223 position (Yasuhiro *et al*, 2012). ONO-WG-307 displays high specificity for BTK given that its IC₅₀ values for related tyrosine kinases (LCK, LYN, FYN) are above 1 μmol/l. The drug exhibits significant activity against the activated B cell-like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL) in TMD-8 mouse xenograft models, with dose-dependent tumour volume growth inhibition of up to 84% over 24 d (Kozaki *et al*, 2011). ONO-WG-307 demonstrates *in vitro* anti-proliferative effects in follicular lymphoma (FL), mantle cell lymphoma (MCL), and chronic lymphocytic leukaemia (CLL) cell lines and its combination with the anti-CD20 antibody rituximab shows promise as an effective combination therapy (Kozaki *et al*, 2011, 2012). To date, no clinical data are available; however, ONO-WG-307's reversible mechanism may result in fewer off-target effects in comparison to irreversible inhibitors.

LFM-A13 (University of Southern California)

LFM-A13 is an intraperitoneally injectable reversible inhibitor of BTK (IC₅₀ = 7.5 μmol/l) that binds to the rectangular catalytic pocket defined by Leu460, Tyr476, Arg525, and Asp539 (Mahajan *et al*, 1999; Uckun *et al*, 2002). LFM-A13 does not affect the enzymatic activity of tyrosine kinases

Table I. Preclinical and phase I study data.

Agent	ONO-WG-307	LFM-A13	Dasatinib	CC-292	Ibrutinib
Developer	ONO Pharmaceutical	University of Southern California	Bristol-Myers Squibb	Celgene Corporation	Pharmacyclics and Janssen Pharmaceuticals
Mechanism, Target	Reversible, Tyr223	Reversible, Unknown	Reversible, Unknown	Irreversible, Cys481	Irreversible, Cys481
Potency	IC ₅₀ = 2 nmol/l	IC ₅₀ = 7.5 μmol/l	IC ₅₀ = 5 nmol/l	IC ₅₀ <0.5 nmol/l	IC ₅₀ = 0.5 nmol/l
Clinical Data From	N/A	N/A	Multiple Histologies	Multiple Histologies	Multiple Histologies
Phase I Trials in			n = 19	n = 17	n = 56
Relapsed/Refractory			ORR 32%, CR 11%	SD: 94%, PR: 6%	(% ORR/CR)
B Cell Malignancies				CLL	MCL: 78/33
				n = 50	CLL/SLL: 69/13
				ORR 34%, CR 0%	FL: 55/27
					DLBCL: 29/0
					WM: 75/0
					MZL: 25/0

B-NHL, B cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinaemia; ORR, objective response rate; CR, complete response; PR, partial response; PFS, progression-free survival; R/R, relapsed/refractory; N/A: not available.

JAK1, JAK3, HCK, epidermal growth factor receptor kinase, and insulin receptor kinase and was shown to increase sensitivity of B-lineage leukaemic cells to ceramide- and vincristine-induced apoptosis *in vitro* (Mahajan *et al*, 1999). In leukaemic mouse models, LFM-A13 was non-toxic when administered at dose levels ranging from 10 to 80 mg/kg and significantly prolonged survival when delivered in combination with vincristine, methylprednisolone, and L-asparaginase (VPL) compared to only VPL therapy (Uckun *et al*, 2002). Preliminary data suggest that chemoresistance in relapsed B cell precursor acute lymphoblastic leukaemia can be overcome with LFM-A13 in combination with chemotherapy (Uckun *et al*, 2011). No clinical data are available to date.

Dasatinib (Bristol-Myers Squibb, New York, NY, USA)

Dasatinib is an orally available, reversible tyrosine kinase inhibitor currently approved for treatment of chronic myeloid leukaemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukaemia (ALL) (Steinberg, 2007). At the time of approval, only BCR-ABL and SRC kinases had been considered as relevant targets, but dasatinib was later discovered to also be a potent inhibitor of BTK ($IC_{50} = 5 \text{ nmol/l}$) *in vitro* with selective activity over ITK (Hantschel *et al*, 2007). Mutation of the gatekeeper residue Thr474 to Ile in BTK confers complete resistance to dasatinib and is suggestive of its mode of interaction with BTK (Hantschel *et al*, 2007).

Preliminary phase I/II data has been reported on 27 patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) (William *et al*, 2010). Patients received dasatinib at doses of 100, 150, or 200 mg once daily for 28-day cycles. The median age was 58 years (range: 34–87), and patients had received a median of 4 (range: 1–20) prior therapies. The maximum tolerable dose (MTD) was determined to be 150 mg. At a median follow up of 24 months, of the 19 evaluable patients the objective response rate (ORR) was 32%: 2 complete responses (CRs), 4 partial responses (PRs), and 8 with stable disease (SD) (Table I). Progression-free

survival (PFS) was 17% at 1 year and 13% at 2 years. Grade 3 and 4 adverse events (AEs) included pleural effusion (22%), thrombocytopenia (19%), neutropenia (11%), anaemia (7%), diarrhoea (7%), leucopenia (4%), rash (4%), weakness/orthostasis (4%), prolonged QTc interval (4%), flash pulmonary oedema (4%), and skin graft failure (4%).

Dasatinib has also been evaluated in a phase II study of R/R CLL (Amrein *et al*, 2011). 15 patients, median age 59 years (range: 40–78) and median 3 prior therapies, were enrolled with a median time on study of 14 weeks. Seventy three percent had either del(11q) or del(17p). 3 patients achieved a PR for an ORR of 20% (Table II). Of the remaining 12 patients, 6 had nodal responses. Grade 3 and 4 haematological toxicities were frequent including neutropenia (67%) and thrombocytopenia (40%). Two patients developed grade 3 pneumonia and four developed pleural effusions. 33% of patients were removed from the study within 4 months due to severe myelosuppression. 73% patients had treatment interrupted at some point in the study due to toxicity.

CC-292 (Celgene Corporation, Summit, NJ, USA)

CC-292, formerly known as AVL-292, is an orally available, potent ($IC_{50 \text{ apparent}} = 0.5 \text{ nmol/l}$, half maximal effective concentration [EC_{50}] = 8 nmol/l), irreversible small molecule inhibitor of BTK that forms a covalent bond with Cys481 (Evans *et al*, 2013). CC-292 displays high levels of specificity for BTK in comparison to other SRC family kinases. The inhibitory activity of CC-292 has been demonstrated in both immunoblot analysis, which revealed that CC-292 strongly inhibits auto-phosphorylation in human naïve primary B cells, and flow cytometry tracking of CD69 upregulation (a surrogate for B cell activation) which exhibited a dose-dependent reduction in CD69 expression with increasing concentrations of CC-292 *in vitro*. Covalent probe analysis of human B cells coupled with enzyme linked immunosorbent assay (ELISA) quantification methods demonstrated 42% BTK occupancy in a 1-h incubation with 10 nmol/l CC-292.

Table II. Clinical data from phase II studies with BTK inhibitors.

Regimen	Disease	n	%ORR (CR)	Outcome
Ibrutinib	CLL, TN	31	67 (2)	26-month PFS: 96%
	CLL, R/R	85	71 (3)	26-month PFS: 75%
	MCL, R/R	111	68 (21)	13.9 months
	GCB DLBCL, R/R	20	5.3 (0)	Median OS: 3.35 months
	ABC DLBCL, R/R	29	40 (8)	Median OS: 9.76 months
Ibrutinib + Ofatumumab	CLL, R/R	27	100 (4)	89% remain on study
Ibrutinib + Bendamustine-Rituximab	CLL, R/R	30	93 (13)	8.1-month PFS: 90%
Dasatinib	CLL, R/R	15	20 (0)	N/A

TN, treatment naïve; R/R, relapsed/refractory; CLL, chronic lymphocytic leukaemia; MCL, mantle cell lymphoma; DLBCL, Diffuse large B cell lymphoma; GCB, Germinal centre B cell, ABC, activated B cell; ORR, objective response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; N/A, not available.

In mice models, % BTK occupancy was positively correlated with reduced signs of arthritic disease.

CC-292 was evaluated in healthy adult subjects and was found to be safe and well tolerated following oral administration at dose levels ranging from 0.5 mg/kg to 7.0 mg/kg. (Evans *et al*, 2011). PK data was reported for the 2.0 mg/kg single oral dose (Evans *et al*, 2013). CC-292 was rapidly absorbed (T_{max} c. 30–120 min), achieving >84% BTK occupancy and mean peak plasma levels (C_{max} = 542 ng/ml) at this dose. The $T_{1/2}$ = 1.9 h, and BTK occupancy was sustained over a 24-h period.

Preliminary phase Ib data with CC-292 was reported on 12 patients with R/R B cell NHL (B-NHL) (8 CLL, 1 DLBCL, 1 FL, 1 marginal zone lymphoma (MZL)) (Brown *et al*, 2012a). Escalating cohorts of 125, 250, and 400 mg/d for 28-day cycles were evaluated. Full BTK occupancy was reached at 250 mg/d and the MTD was >400 mg/d. The median age of patients was 68 years (range: 45–79), median number of prior therapies 2.5 (range: 1–10), and reported median time on treatment was 65 d. While the duration of response (DOR) was not available at the time of the report, 10 of the 12 patients were continuing on treatment. All 8 CLL patients had SD with a median 28% decrease from baseline lymph node measurement. The MZL patient also had SD. The DLBCL patient had progressive disease (PD) and the FL patient was not evaluable due to dose limiting toxicity (DLT). The drug was generally well tolerated with no grade 4 AEs reported and only a single grade 3 AE of a low absolute neutrophil count, probably treatment-related.

Updated results were recently presented on 86 patients (23 B-NHL, 6 Waldenström macroglobulinaemia (WM), 57 CLL/small lymphocytic lymphoma (SLL)) treated with CC-292 at doses of 125, 250, 400, 625, 750, and 1000 mg QD or 375 and 500 mg BID (Table 1) (Brown *et al*, 2013). An expansion cohort of CLL patients at 750 mg QD was also tested. All patients received continuous dosing in 28-day cycles until PD or intolerable toxicity. The median age was 65 years (range: 29–89) and median number of prior therapies 3 (range: 1–12). Of the 57 CLL patients, 39 (68.4%) had at least 1 high risk factor, including 30 (52.6%) with unmutated *IGHV*, and 26 (45.6%) with del11q22 ($n = 12$), del17p ($n = 14$), or both ($n = 2$). The median time on therapy was 144 d (range: 13–515). Three DLTs were reported, including thrombocytopenia (400 mg), pneumonitis (1000 mg), and altered mental status (500 mg BID). The MTD has not been reached. The most frequent treatment emergent AEs ($\geq 10\%$ of patients regardless of causality) were grade 1–2.

All 17 efficacy-evaluable B-NHL patients had SD except for a single PR in a patient with MZL who started at 250 mg and escalated sequentially up to 750 mg QD, achieving a PR at cycle 16. Of 50 efficacy-evaluable CLL patients, 17 (34%) achieved a PR and 24 (45%) showed lymph node reduction. Lymphocytosis, a class effect of these agents (discussed under the ibrutinib section) was noted in 10 patients and resolved in 5 patients. At the time of reporting, the median duration

of treatment was 176 d (range: 16–473), and 2 CLL patients had been on treatment for over 15 cycles, both initiating treatment at 400 mg QD and experiencing nodal reductions of 32% and 27%.

The ORR was 31% at 750 mg QD, 50% at 1000 mg QD and 66.7% at 375 mg BID, suggesting that BID dosing maybe more efficacious. Most patients at 500 mg BID were not eligible for response evaluation at the time of publication. Among the responding patients, poor risk factors included unmutated *IGHV* ($n = 8$), del11q ($n = 3$), and/or del17p ($n = 2$) suggesting efficacy in these subgroups.

Currently there is an ongoing phase Ib study of CC-292 in combination with lenalidomide in patients with R/R B cell lymphoma, but no data has been reported to date.

Ibrutinib (PCI-32765) (Pharmacyclics, Inc., Sunnyvale, CA, USA and Janssen Pharmaceuticals, Inc., Titusville, NJ, USA)

Ibrutinib is the most advanced of the BTK inhibitors in clinical development (Burger & Buggy, 2013). It is an orally available, potent ($IC_{50} = 0.5$ nmol/l), irreversible inhibitor of BTK that forms a covalent bond with Cys481 (Honigberg *et al*, 2010). *In vitro*, treatment of DOHH2 cells with ibrutinib prevents phosphorylation of BTK's immediate substrate PLC γ 2 and the further downstream kinase ERK, while not affecting upstream kinases like SYK. Specificity for BTK was confirmed by showing a lack of significant activity against a sample of 19 other related kinases, including seven kinases that share the cysteine residue targeted by ibrutinib. BTK occupancy can be measured with a fluorescently tagged affinity probe, PCI-33380, which consists of the core inhibitor molecule linked with a Bodipy FL fluorophore via a piperazine linker. Levels of irreversible probe binding to BTK can be detected by denaturing gel electrophoresis and fluorescent gel staining of BTK-transfected cell lysates treated with PCI-33380 such that increased target occupancy by drug results in lower probe signalling (Honigberg *et al*, 2010). Continuous exposure to ibrutinib inhibits upregulation of CD69 while maintaining over 1000-fold selectivity for B cells over T cells (Honigberg *et al*, 2010).

In vivo data confirmed the therapeutic potential of the drug (Honigberg *et al*, 2010). In mice models, reduction in signs of arthritic disease correlated with levels of inhibition of BTK by ibrutinib and was marked by reductions in production of anticollagen autoantibodies and total IgG levels. Similarly, in canine models with both naïve and previously treated naturally occurring B-NHL, objective clinical responses were achieved with full BTK occupancy at dosages of 2.5–20 mg/kg/d.

In a phase Ia dose escalation trial, 56 patients with R/R B-NHL of variable histologies (16 FL, 16 CLL/SLL, 9 MCL, 7 DLBCL, 4 MZL, and 4 WM) were enrolled to determine MTD, safety, PK/pharmacodynamics and tumour response (Advani *et al*, 2013). MTD was defined as a dose three levels

above the dose level with full BTK occupancy, as measured by a fluorescent affinity probe. Two dosing schedules were evaluated: 35-day cycles with 28 d on and 7 d off and a once daily continuous dosing. The median age of patients was 65 years (range: 41–82), median number of prior therapies was 3 (range: 1–10), and median treatment time was 5 cycles. Ibrutinib was tolerable at doses of 1.0–12.5 mg/kg/d with no DLTs. Pharmacodynamic studies using the competitive binding assay with a fluorescent probe showed that 1.25 mg/kg/d of ibrutinib achieved sustained BTK engagement over 24 h and 2.5 mg/kg/d achieved near complete BTK engagement at 4 and 24 h post-dosing. PK data suggested that at dose levels of 1.25 mg/kg/d, the C_{max} = 82 ng/ml, T_{max} median = 1.14 h, and $T_{1/2}$ = 4.92 h (Pollyea *et al*, 2009). Ibrutinib was well tolerated with the majority of AEs being mainly grade 1 or 2 with limited occurrences of grade 3 and 4 toxicities including neutropenia (12.5%), thrombocytopenia (7.2%), and anaemia (7.1%). Only two DLTs were reported, a grade 3 allergic reaction in a patient with a history of similar reactions and a dose interruption for more than 7 d due to transient grade 2 neutropenia. Continuous dosing was just as effective as the interrupted dosing schedule in terms of PK/pharmacodynamics and a fixed dose of 560 mg/d was identified as the dose to move forward with in phase II trials.

Efficacy data was reported on 50 evaluable patients with an ORR of 60% (CR 16%) (Advani *et al*, 2013). Responses were noted across histologies: MCL (7 of 9 patients, 3 CRs), CLL/SLL (11 of 16 patients, 2 CRs), FL (6 of 16 patients, 3 CRs), DLBCL (2 of 7 patients), WM (3 of 4 patients), and MZL (1 of 4 patients) (Table I). The median PFS was 13.6 months and 20 patients remained on treatment at the time of the report.

Consistent with observations of other agents that affect BCR signalling inhibition in patients with CLL and MCL, along with nodal shrinkage there was a simultaneous dramatic spike in plasma lymphocyte levels occurring in cycles 1 and 2 of treatment with ibrutinib which slowly declined and stabilized over time (Herman *et al*, 2011; Brown, 2012). The apparent increase in lymphocyte counts was a result of the egress of CLL cells from the lymph nodes and recirculation in the blood (Brown, 2012). BCR signalling is implicated in integrin-mediated adhesion of cells to fibronectin and, therefore, inhibition reduces cellular retention within the tumour microenvironment (Herman *et al*, 2011).

An update of the 16 patients with FL treated in the phase I study has also been reported (Fowler *et al*, 2012). The median age was 60 years (range: 41–71) with a median of 3 prior therapies (range: 1–5). The Follicular Lymphoma International Prognostic Index (FLIPI) scores were high in 44% of patients and intermediate in 38%. Of the 11 patients that received treatment with a dose of 2.5 mg/kg or higher (the minimum dose necessary for full BTK occupancy), 3 patients achieved a CR and 3 a PR for an ORR of 54.5%. The DOR was 12.3 months with a median PFS of 13.4 months. The 9

patients treated at doses of at least 5 mg/kg had a median PFS of 19.6 months with 2 patients remaining on the study at 25 and 29 months.

Collectively, these phase I results suggest that ibrutinib is well tolerated and has significant activity in a variety of histologies (Brown, 2013). These data have led to several phase II studies evaluating its efficacy in specific B cell histologies (Table II).

Phase II studies with ibrutinib

Relapsed/refractory chronic lymphocytic leukaemia and small lymphocytic lymphoma

In a phase Ib/II study, 85 patients (median age 64 years) with R/R disease were enrolled in three cohorts, with 51 patients receiving 420 mg/d and 34 patients receiving 840 mg/d in 28-day cycles (Byrd *et al*, 2013). Median number of prior treatments was 4 (range: 1–12). Of note, 52% of patients had bulky adenopathy (>5 cm), 33% had 17p deletion, and 81% unmutated *IGHV*. The ORR was 71% (4% CR) in the 420 mg cohorts and 71% (0% CR) in the 820 mg cohort. A nodal PR (defined as a >50% reduction in total lymph node size) with lymphocytosis was seen in 20% and 15% of patients in the 420 mg and 840 mg cohorts respectively. The lymphocytosis resolved over time. 13% of patients had PD while taking ibrutinib. The estimated 26 months PFS was 75%. The best response was very similar across the two doses and therefore 420 mg was selected as the dose for future evaluation. Ibrutinib was well tolerated and the majority of reported AEs were grade 2. The most common grade ≥ 3 AEs were pneumonia (12%) and dehydration (6%). Grade ≥ 3 haematological toxicities were limited: anaemia (6%), neutropenia (15%), and thrombocytopenia (6%).

Therapy naïve chronic lymphocytic leukaemia

A phase Ib/II study evaluated treatment of naïve elderly CLL patients (≥ 65 years) (Byrd *et al*, 2012a). 31 patients were enrolled in two cohorts with 26 patients receiving 420 mg/d and 5 receiving 840 mg/d in 28 d cycles. The 840 mg cohort was eventually discontinued due to improved safety of the 420 mg dose and comparable efficacy (Byrd *et al*, 2012b). The median age was 71 years (range: 65–84) and 55% of patients had unmutated *IGHV*. In the 420 mg cohort at a median 16.6 months follow-up, the ORR was 71% (10% CR), with an additional 10% of patients achieving PR with lymphocytosis. The 22-month estimated PFS was 96%. The majority of AEs were grade 2, easily managed, and included diarrhoea, fatigue, upper respiratory tract infection, rash, nausea and arthralgias. Grade ≥ 3 haematological AEs were infrequent.

The very promising single agent activity and tolerability of ibrutinib in CLL have paved the way for trials in combination with chemoimmunotherapy or obviating the need for

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