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R&D INSIGHT REPORT

Ibrutinib: First Global Approval

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Abstract Ibrutinib (Imbruvica™) is a small molecule, first-in-class, once-daily, orally available, Bruton's tyrosine kinase inhibitor that is under development for the treatment of B cell malignancies, including chronic lymphocytic leukaemia (CLL), mantle cell lymphoma (MCL) and diffuse large B cell lymphoma (DLBCL), as well as multiple myeloma (MM), follicular lymphoma (FL) and Waldenstrom's macroglobulinemia (WM). It has been developed by Pharmacyclics, Inc. and Janssen Biotech, Inc. Ibrutinib acts by blocking B-cell antigen receptor signalling, thereby reducing malignant proliferation of B cells and inducing cell death. Based chiefly on findings from a phase Ib/II study, ibrutinib has been approved in the USA for the treatment of MCL in previously treated patients and is one of the first approvals through the US FDA's Breakthrough Therapy Designation Pathway. An application has been filed in the EU seeking regulatory approval in this indication. In both the USA and EU, further applications have been filed with regulatory bodies seeking approval for the use of ibrutinib in patients with previously treated CLL/small lymphocytic lymphoma (SLL). Phase III trials are underway worldwide to evaluate ibrutinib in the treatment of patients with CLL/SLL, DLBCL and MCL, and the agent is in phase II development for use in WM, FL and MM. This article summarizes the milestones in the development of ibrutinib leading to its first approval in MCL.

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

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1 Introduction

B cell lymphomas are the most common haematological cancers in adults and account for ≈85 % of all cases of non-Hodgkin lymphoma (NHL) [1]. Diffuse large B cell lymphoma (DLBCL) is the most common B cell lymphoma in the US, with an incidence of 7.14 per 100,000 person-years, followed by chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) and follicular lymphoma (FL), with incidences of 5.17 and 3.18 per 100,000 person-years, respectively; the incidence of mantle cell lymphoma (MCL) and Waldenstrom's macroglobulinaemia (WM) were lower at 0.51 and 0.35 per 100,000 person-years [2].

These malignancies have a markedly variable clinical course, ranging from indolent to rapidly progressive disease, and treatment is individualized according to the lymphoma type, disease stage and risk profile of each patient [3–6]. In recent years, various molecular mediators of pathogenesis have been identified and these have opened up new possibilities for treatment [6]. Among these molecular mediators is Bruton's tyrosine kinase (BTK), which is essential for B cell receptor (BCR) signaling [7]. Aberrant BCR signaling, in association with antigen-dependent activation, is thought to be involved in the pathogenesis of several B cell malignancies, including MCL and certain subgroups of DLBCL [7]. Thus, BTK is an important potential target for treatment and the BTK inhibitor ibrutinib (Imbruvica™) is the first such agent to

Features and properties of ibrutinib

Alternative names	Imbruvica™; PCI 32765; PCI-32765; PCI32765
Class	Small-molecule inhibitor of Bruton's tyrosine kinase (BTK)
Mechanism of action	Irreversible inhibition of BTK
Pharmacodynamics	Inhibition of the proliferation and survival of malignant B cells and of their migration and substrate adhesion
Route of administration	Oral
Pharmacokinetics	Reaches maximum concentration in plasma in 1–2 h and is widely distributed in the body. Metabolized by hepatic cytochrome P450 3A enzymes and eliminated chiefly as metabolites in the faeces, with an elimination half-life of 4–6 h
Most frequent adverse events	
All grades	Mantle cell lymphoma: diarrhoea, fatigue, nausea, peripheral oedema, dyspnoea, constipation, upper respiratory tract infection (URTI), vomiting, decreased appetite
	Chronic lymphocytic leukemia: diarrhoea, URTI, fatigue, cough, arthralgia, rash, pyrexia
Grades 3/4	Pneumonia, dehydration, neutropenia, thrombocytopenia, anaemia
ATC Codes	
WHO ATC code	L012X-E (Protein kinase inhibitors)
EphMRA ATC code	L1X4 (Antineoplastic protein kinase inhibitors)
Chemical name	1-{(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo [3,4-*d*] pyrimidin-1-yl] piperidin-1-yl] prop-2-en-1-one

be approved for use in a patient group with B cell lymphoma [8].

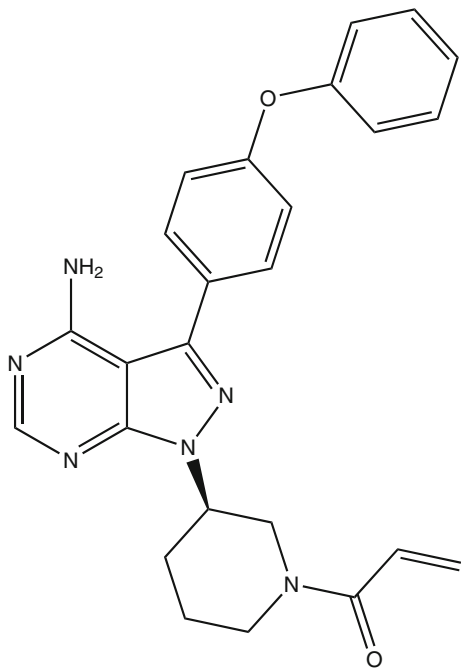
Ibrutinib is presumed to act by blocking B cell antigen receptor signalling, thereby reducing malignant B cell proliferation and inducing cell death [8, 9]. It was selected as a lead compound from a research programme acquired from Celera (a subsidiary of Quest Diagnostics) and has been approved in the USA for the treatment of MCL in previously treated patients [8]. Approval was based on an improvement in the response rate, as improvement in survival or disease-related symptoms has not yet been established [8]. This is one of the first approvals through the US FDA's Breakthrough Therapy Designation Pathway. An application has also been filed in the EU seeking regulatory approval in this indication. Further US and EU applications have been filed seeking approval for the use of ibrutinib in patients with relapsed/refractory CLL/SLL [10, 11]. Preclinical studies have also been conducted to assess its promise as a treatment for breast cancer.

This article provides an overview of the development and clinical pharmacology of ibrutinib in various haematological malignancies.

1.1 Company Agreements

Pharmacyclics acquired the technology and intellectual property rights to the ibrutinib programme from Celera Genomics Group (later Celera Corporation) in April 2006. Prior to the sale of the programme to Pharmacyclics, Celera Group had reached lead optimisation stage and had identified orally bioavailable compounds that inhibit BTK [12–14]. Quest Diagnostics subsequently acquired Celera in May 2011 [15].

In August 2011, Pharmacyclics signed a 5-year Cooperative Research and Development Agreement with the National Cancer Institute (NCI) to collaborate on the development of ibrutinib for the treatment of haematological malignancies. Under the terms of the agreement, the NCI's Division of Cancer Treatment and Diagnosis was to sponsor phase I and II trials in various haematological malignancies, including NHL and multiple myeloma (MM) [16]. In December 2011, Janssen Biotech executed an agreement with Pharmacyclics to jointly develop and commercialize ibrutinib.



Chemical structure of ibrutinib

1.1.1 Manufacturing Agreements

In November 2013, WuXi PharmaTech's subsidiary, Shanghai SynTheAll Pharmaceutical, entered into an agreement with Pharmacyclics for the clinical and commercial supply of ibrutinib. Pharmacyclics previously had a multi-year development and clinical manufacturing partnership with this company, which supported Pharmacyclics with NDA submission and approval of ibrutinib by the US FDA. No Form 483 observations were issued by the FDA during the GMP pre-approval inspection of WuXi's manufacturing facilities. WuXi PharmaTech's subsidiaries operate as WuXi AppTec [17].

2 Scientific Summary

2.1 Pharmacodynamics

The BCR pathway is an important regulator of B cell differentiation, migration, proliferation and apoptosis and is thought to be important in the development of B cell malignancies [7, 9]. BTK is operative early in the BCR cascade and BTK null mutations are associated with selective B cell inhibition and lowered serum immunoglobulin (X-linked agammaglobulinaemia) [7, 9]. Thus, agents targeting BTK offer promise for the treatment of B cell malignancies. Ibrutinib irreversibly inhibits BTK through its covalent bond with the cysteine Cys-481 of BTK [7]. In doing so, it inhibits proliferation and survival of malignant B cells, as well as reducing their migration and substrate adhesion [8]. Although BTK is not found in T cells, ibrutinib may also find a place in the treatment of T cell-mediated diseases, as in a recent investigation, ibrutinib was an inhibitor of interleukin-2-kinase, which has a key role in T cell signalling [18].

In dogs with canine lymphoma, ibrutinib completely occupied BTK in blood and in tumour tissue [19]. In other preclinical studies, it inhibited growth of BCR-expressing human lymphoma cell lines [20, 21], and according to a preliminary report, was synergistic with Nimbus Discovery IRAK-4 inhibitors, ND 2110 and ND 2158 in animal models of DLBCL [22]. In breast cancer cell lines, ibrutinib inhibited ErbB phosphorylation, downstream AKT, MEK and ERK phosphorylation and cell growth in ErbB2 over-expressing and gene-amplified cell lines [23]. Ibrutinib was synergistic with abexinostat (an HDAC inhibitor) in mice bearing solid tumours, including non-small cell lung cancer [24].

Based on interim results pertaining to MM disease markers in a phase II study (NCT01478581), ibrutinib inhibited the interaction of MM cells with stromal cells, inhibited growth of MM colony-forming cells from patient explants, suppressed osteoclast differentiation, and reduced cytokine and chemokine production [25]. It also decreased disease progression and bone destruction in an animal model of MM [25].

In a phase I study in patients with relapsed or refractory NHL, ibrutinib completely occupied BTK, with occupancy >95 % at 4 h post-dose, but without significant depletion of peripheral blood B, T or natural killer cells, and without alteration of T cell responses [26].

In preliminary findings from a clinical trial in patients with previously treated MM ($n = 7$), ibrutinib 420 mg/day was associated with reductions in some markers of bone metabolism (including sclerostin and RANKL) and pro-angiogenic and growth factors, along with reductions in blood levels of cytokines and reduced chemokine turnover [25].

The anticancer actions of ibrutinib observed in phase II studies are discussed in Sect 2.3.

2.2 Pharmacokinetics

Ibrutinib is rapidly absorbed after oral administration, with systemic exposure increasing with doses up to 840 mg [8]. The maximum ibrutinib plasma concentration is reached in 1–2 h and the steady-state area under the concentration-time curve was 953 ng·h/mL at a dosage of 560 mg/day. Ibrutinib systemic exposure increased ≈2-fold after administration with food compared to administration in a fasted state. It is recommended that ibrutinib is taken with water at the same time each day [8].

The apparent steady-state volume of distribution of ibrutinib is ≈10,000 L, indicating that it is widely distributed in the body [8]. Ibrutinib is 97.3 % reversibly bound to human plasma protein, with no concentration dependence in the range of 50–1,000 ng/mL [8].

Ibrutinib is metabolized by hepatic cytochrome P450 (CYP) 3A enzymes and to a minor extent by CYP2D6 [8]. Metabolism is the major route of elimination. The dihydrodiol metabolite PCI-45227 is active but with activity toward BTK that is ≈15-fold lower than that of the parent compound. At steady state, the ratio for the mean concentration of PCI-45227 to ibrutinib is 1:2.8. The ibrutinib apparent clearance is ≈1,000 L/h and the elimination half-life is 4–6 h. Ibrutinib is chiefly eliminated in the faeces, with <10 % excreted in the urine, and is almost entirely eliminated as metabolites [8].

Ibrutinib clearance is not altered by age (37–84 years) or gender [8]. Preliminary data in patients with hepatic impairment suggest that ibrutinib systemic exposure is ≈6-fold higher in patients with moderate hepatic impairment. Ibrutinib is not cleared significantly by the kidneys and, in subjects with creatinine clearance (CL_{CR}) >25 mL/min, there was no relationship between the CL_{CR} and

ibrutinib exposure. There are no pharmacokinetic data in patients with severe renal impairment (CL_{CR} <25 mL/min) or in patients receiving dialysis [8].

Ketoconazole (a strong CYP3A inhibitor) increased the ibrutinib maximum concentration and AUC by 29- and 24-fold, respectively; moderate CYP3A inhibitors may increase the AUC by 6- to 9-fold [8]. Clinicians should avoid coadministering ibrutinib with moderate and strong CYP3A inhibitors [8]. If ibrutinib must be used with a moderate CYP3A inhibitor, the ibrutinib dosage should be decreased. Clinicians should consider interrupting the administration of ibrutinib during short-term use of CYP3A inhibitors and should avoid long-term use of CYP3A inhibitors, altogether [8].

Clinicians should also avoid coadminstration with CYP3A inducers [8]. Rifampin (a strong CYP3A inducer) can decrease ibrutinib exposure 10-fold, while moderate CYP3A inducers may reduce exposure by up to 3-fold [8].

As ibrutinib and its active metabolite are weak inducers of CYP enzymes, ibrutinib at therapeutic dosages is unlikely to have clinically important effects on the pharmacokinetics of CYP substrates [8].

2.3 Therapeutic Trials

In a phase I study in patients with various relapsed/refractory B cell malignancies ($n = 50$) (NCT00849654), ibrutinib 1.25–12.5 mg/kg/day was associated with an overall response rate (ORR) of 60 % across all histologies, including in 16 patients (69 %) with CLL or SLL; in 11 of the patients with CLL, all had rapid reductions in lymphadenopathy with the first treatment and only one patient did not meet response criteria [9]. Patients with CLL also had an increase in the absolute lymphocyte count, suggesting egress of malignant cells into blood. Among other lymphoma types, 6 of 16 patients with FL had a response, as did 2 of 7 patients with DLBCL, 7 of 9 with MCL (78 %) and 3 of 4 with WM [9].

2.3.1 Mantle Cell Lymphoma (MCL)

In a phase II study (NCT01236391), patients with relapsed or refractory MCL who had had a median of three prior anticancer therapies were treated with oral ibrutinib 560 mg/day [27]. Among patients who received at least one dose ($n = 111$), the ORR was 68 % (47 % with a partial and 21 % with a complete response, according to Revised International Working Group Criteria for non-Hodgkin's lymphoma). Results were similar for patients previously treated with bortezomib or who were bortezomib-naive. For the 75 patients who responded, the median time to response was 1.9 months (5.5 months to complete response) and the median response duration was 17.5 months. For all patients, the median progression-free survival (PFS) was 13.9 months. In keeping with expectations that ibrutinib would mobilize MCL cells from tissues to peripheral blood, in some patients, there was an increase in MCL cells in blood 10 days after treatment initiation, with a subsequent decline in these cells to near baseline by day 28 [27]. This study provided the basis for the US FDA approval of ibrutinib in MCL [8].

2.3.2 Chronic Lymphocytic Leukaemia (CLL) or Small Lymphocytic Lymphoma (SLL)

Deletion 17p is associated with a poor prognosis in CLL [28]. Preliminary findings from a phase II study (NCT01744691) of ibrutinib 420 mg/day in patients with treatment-naïve or relapsed or refractory CLL with deletion 17p ($n = 25$ evaluable patients) were promising, as 88 % had a nodal response, with a median 70 % reduction in lymph node size, 40 % had a partial response and 40 % had a partial response with lymphocytosis. All patients had reduced splenomegaly, and tumour burden was also reduced, as assessed by immunohistochemistry for CD79a in bone marrow biopsies [28].

In an open-label, phase Ib/II multicentre study (NCT01105247), patients with relapsed or refractory CLL/SLL were treated with ibrutinib 420 ($n = 51$) or 840 ($n = 34$) mg/day [29]. The ORR was 71 % (34 partial and 2 complete responses) with ibrutinib 420 mg/day and 71 % with 840 mg/day (24 partial responses). There was no relationship between responses and Rai disease stage, number of prior therapies, or genetic risk (deletion17p13.1) [29].

In a further phase Ib study in which patients with relapsed or refractory CLL/SLL received ibrutinib 420 mg/day and up to 6 cycles of bendamustine plus rituximab ($n = 30$), the ORR was 93 % and the estimated 12-month PFS was 90 % [30].

In a single-centre study in patients with CLL high-risk disease features (deletion 17p or TP53 mutation, or PFS <36 months after frontline chemotherapy, or relapsed with deletion 11q), patients were treated with ibrutinib 420 mg/day plus rituximab therapy [31, 32]. At the most recent follow-up, 3 of 39 evaluable patients had a complete response and 34 had a partial response, yielding an ORR of 95 %; in patients with deletion 17p or TP53 mutation ($n = 20$), the ORR was 90 % [32].

The results are consistent with preliminary findings from another phase II single-centre study (NCT01500733) of ibrutinib in treatment-naïve or previously-treated patients with CLL, with and without deletion 17p [33]. For the first 53 patients (median follow-up 14 months), the estimated event-free survival at 14 months was 93 %; 66 % of patients had a partial response and 28 % a partial response

Key clinical trials of ibrutinib (trials with citations have interim or final results)

Drugs	Indication	Study phase	Study status	Study location	Trial identifiers[a]	Sponsor
Ibrutinib vs. ofatumumab	Chronic lymphocytic leukaemia (relapsed/refractory)	III	Enrolment completed	USA, EU, Australia	NCT01578707 (PCYC-1112)	Pharmacyclics
Ibrutinib [29]	Chronic lymphocytic leukaemia (relapsed/refractory)	Ib/II	Completed	USA	NCT01105247 (PCYC-1102)	Pharmacyclics
Ibrutinib + bendamustine + rituximab vs. bendamustine + rituximab	Chronic lymphocytic leukaemia (relapsed/refractory	III	Recruiting	Global	NCT01611090 (CLL-3001)	Janssen Research & Development
Ibrutinib vs. chlorambucil	Chronic lymphocytic leukaemia (previously untreated elderly patients)	III	Recruiting	Global	NCT01722487 (PCYC-1115/6)	Pharmacyclics
Ibrutinib	Chronic lymphocytic leukaemia (relapsed/refractory with del 17p)	II	Enrolment completed	USA, EU, Australia, New Zealand	NCT01744691 (PCYC-1117)	Pharmacyclics
Ibrutinib vs. rituximab	Chronic lymphocytic leukaemia (relapsed/refractory)	III	Recruiting	Asia-Pacific	NCT01973387 (CLL-3002)	Janssen Research & Development
Ibrutinib + rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP)	Diffuse large B cell lymphoma non-germinal centre B cell-like subtype (previously untreated)	III	Recruiting	Global	NCT01855750 (DBL-3001)	Janssen Research & Development
Ibrutinib [35, 36]	Diffuse large B cell lymphoma non-germinal centre B cell-like subtype (relapsed/refractory)	II	Recruiting	USA	NCT01325701 (PCYC-1106)	Pharmacyclics
Ibrutinib	Follicular lymphoma (relapsed/refractory)	II	Recruiting	USA, EU, Australia	NCT01779791 (FLR-2002)	Janssen Research & Development
Ibrutinib + bendamustine + rituximab or ibrutinib + R-CHOP	Indolent non-Hodgkin's lymphoma (relapsed/refractory)	III	Not yet recruiting	Global	NCT01974440 (FLR-3001)	Janssen Research & Development
Ibrutinib vs. temsirolimus	Mantle cell lymphoma (relapsed/refractory)	III	Recruiting	Global	NCT01646021 (MCL-3001)	Janssen Research & Development
Ibrutinib + bendamustine + rituximab vs. bendamustine + rituximab	Mantle cell lymphoma (previously untreated)	III	Recruiting	Global	NCT01776840 (MCL-3002)	Janssen Research & Development
Ibrutinib [27]	Mantle cell lymphoma (relapsed/refractory)	II	Enrolment completed	USA, EU	NCT01236391 (PCYC-1104)	Pharmacyclics
Ibrutinib [25]	Multiple myeloma (relapsed/refractory)	II	Recruiting	USA	NCT01478581 (PCYC-1111)	Pharmacyclics
Ibrutinib [37]	Waldenstrom's macroglobulinemia (relapsed/refractory)	II	Enrolment completed	USA	NCT01614821	Dana-Farber Cancer Institute

[a] Trial aims and design features are available at http://clinicaltrials.gov/

with lymphocytosis. Response rates were higher in patients without than with deletion 17p, but there was no difference between these groups in clinical benefit or disease control [33].

In a follow-up of patients from the phase Ib/II study and from a phase I ascending dose study, ($n = 140$ in the efficacy population), after a median duration of treatment of 27.2 months, the median duration of response had not

been reached; by the 30-month landmark, 76.1 % of patients were alive without disease progression [34].

2.3.3 Diffuse Large B Cell Lymphoma (DLBCL)

Interim results from an open-label, phase II study (NCT01325701) indicate that ibrutinib has preferential activity in the activated B cell (ABC) subtype of DLBCL [35, 36]. In this study patients with DLBCL received ibrutinib 560 mg/day until disease progression. The ORR was 41 % in patients with the ABC subtype of DLCBL ($n = 29$) and 5 % in the germinal centre B cell-like (GCB) subtype ($n = 20$). There were 5 complete responses in patients in the ABC subtype and none in the GCB subtype [36].

2.3.4 Waldenstrom's Macroglobulinemia (WM)

MYD88 L265P is a mutation that occurs in >90 % of patients with WM [37]. Tyrosine kinase inhibitors are expected to be efficacious in WM, as BTK activates downstream MYD88 L265P/IRAK-d NF-kB-mediated pathways that support the growth and survival of WM tumour cells [37]. In a phase II, prospective, multicentre study (NCT01614821) that included 63 patients with symptomatic WM with ≥1 prior treatment, the best ORR (minor response or better) was 81 %; 57 % had a partial response or better, with a median time to response of 4 weeks [38]. At best response, the median serum IgM level was reduced from 3,610 to 1,340 mg/dL and the M-protein level from 2.14 to 0.84 g/dL (both $p < 0.00001$ vs. baseline). The median haematocrit increased from 30.8 to 38.1 % and the median haemaglobin level from 10.5 to 12.6 g/dL (both $p < 0.00001$ vs. baseline) [38].

2.4 Adverse Events

2.4.1 In Patients with MCL

In the fully published phase II study (NCT01236391), patients received ibrutinib 560 mg/day for a median treatment period of 8.3 months ($n = 111$) [8, 27]. Most adverse events were grade 1 or 2 in severity. Treatment-emergent adverse events reported in more than 20 % of patients included diarrhoea (50 %), fatigue (41 %), nausea (31 %), peripheral oedema (28 %), dyspnoea (27 %), constipation (25 %), upper respiratory tract infection (23 %), vomiting (23 %) and decreased appetite (21 %). The only grade 3 or higher treatment-emergent non-haematological adverse event reported in ≥5 % of patients was pneumonia (6 %). Grade 3 or higher haematological events were neutropenia (16 %), thrombocytopenia (11 %) and anaemia (10 %) [27].

Eight patients discontinued treatment as a result of adverse events [27]. In total, 16 patients died during the study, 12 patients as a result of disease progression and 4 patients with adverse events, including 2 patients with pneumonia, 1 with sepsis and 1 with cardiac arrest that was not thought to be drug-related [27].

2.4.2 In Patients with CLL or SLL

In the fully published phase Ib/II study (NCT01105247), patients received ibrutinib 420 ($n = 51$) or 840 ($n = 34$) mg/day for a median time on treatment of 21.0 months [29]. The majority of adverse events were grade 1 or 2. The most common adverse events occurring in >20 % of patients were diarrhoea (49 %), upper respiratory tract infection (33 %), fatigue (32 %), cough (31 %), arthralgia (27 %), rash (27 %), pyrexia (27 %) and peripheral oedema (21 %). The most common ≥grade 3 adverse events were neutropenia (15 %), pneumonia (12 %) and dehydration (6 %). Grade 3 or 4 infections generally occurred early in treatment (i.e. in the first 6 months). During follow-up to assess survival, 7 patients discontinued or died, including 3 patients with pneumonia, 2 with sepsis, 1 with bacteraemia and 1 with a gastrointestinal hemorrhage (this patient had a pre-treatment bleeding diathesis and died 292 days after treatment discontinuation) [29].

In a follow-up of patients from the above study and from a phase I ascending dose study ($n = 148$), after a median follow-up of 21.5 months, 109 (74 %) patients continued treatment for ≥1 year and the serious adverse event rate was 43 % in the first year of treatment and 32 % after the first year [34]. In all, 12 (8 %) patients discontinued treatment in the first year and 6 of 109 (6 %) patients discontinued treatment after the first year. The most frequent ≥grade 3 adverse events were pneumonia (16.9 %), hypertension (13.5 %), neutropenia (11.5 %), thrombocytopenia (7.4 %) and diarrhoea (5.4 %) [34].

2.4.3 Other Adverse Events

The US PI contains warnings and precautions regarding a possible increased risk of risk of haemorrhage, infections, myelosuppression, renal toxicity and second primary malignancies with ibrutinib [8]. Although the causal mechanisms linking ibrutinib to these adverse events are not necessarily understood, serious adverse events of these types have been observed in patients treated with ibrutinib. Patients should be monitored for these adverse events, including monitoring of haematological and renal function. In patients at risk for bleeding, the risks and benefits of ibrutinib need to be weighed before starting treatment. Animal studies suggest that ibrutinib could cause foetal harm if administered to a pregnant woman. Therefore,

women are advised not to become pregnant while taking ibrutinib [8].

2.5 Ongoing Trials

In light of findings from preclinical and the phase I/II studies already discussed, phase II or III studies of ibrutinib have been initiated in MCL, CLL, DLCBCL, FL, WM, indolent NHL and MM. For the ongoing phase II studies, the ORR is generally the primary efficacy endpoint. The ongoing phase III trials are multicentre or multinational trials that identify either PFS or event-free-survival as the primary efficacy endpoint.

2.5.1 In MCL

- NCT01646021 (RAY) is a randomized, open-label, phase III trial that will compare ibrutinib 560 mg/day with therapy with temsirolimus in patients with relapsed/refractory MCL. The trial was initiated in December 2012 and will recruit ≈280 patients.
- NCT01776840 (SHINE) is a randomized, double-blind phase III trial that will compare ibrutinib 560 mg/day in combination with bendamustine plus rituximab versus bendamustine plus rituximab plus placebo in elderly patients (age ≥65 years) with relapsed/refractory MCL. The trial was initiated in March 2013 and will recruit ≈520 patients.
- NCT01599949 (SPARK) is an open-label phase II study in patients with MCL who have received at least one rituximab-containing chemotherapy regimen and who have had disease progression despite bortezomib. Initial enrolment was completed in April 2013.

2.5.2 In CLL/SLL

- NCT01578707 (RESONATE) is a randomized, open-label, phase III trial in relapsed/refractory patients that will compare ibrutinib 420 mg/day with therapy with ofatumumab. The trial has recruited the planned 391 patients and data from a pre-planned interim analysis are expected early in 2014.
- NCT01611090 (HELIOS) is a double-blind, phase III trial in relapsed/refractory patients that will compare ibrutinib 420 mg/day in combination with bendamustine and rituximab versus bendamustine and rituximab plus placebo. The trial was initiated in the first half of 2012 and will recruit ≈580 patients.
- NCT01722487 (RESONATE-2) is an open-label phase III trial in previously untreated elderly patients 65 years and older that will compare ibrutinib 420 mg/day with therapy with chlorambucil. This trial was initiated in December 2013 and will recruit ≈272 patients.
- NCT01744691 (RESONATE-17) is an open-label, single-arm, phase II study of ibrutinib in relapsed/refractory patients with deletion 17p. Data will be available from this study in 2014.
- NCT01973387 is a phase III trial underway in Asia-Pacific in patients with relapsed/refractory CLL and will compare ibrutinib 420 mg/day with rituximab. The trial will recruit ≈150 patients.

2.5.3 In DLBCL

- NCT01855750 (PHOENIX) is a randomized, double-blind, phase III trial that will compare ibrutinib 560 mg/day in combination with rituximab, cyclophosphamide plus doxorubicin plus vincristine plus prednisone (R-CHOP) versus R-CHOP plus placebo in patients with newly diagnosed and untreated non-GCB DLBCL subtype. This trial was initiated in September 2013 and will recruit ≈800 patients.
- NCT01325701 is an ongoing phase II study with preliminary results (Sect. 2.3.3). Enrolment in this trial has been expanded, which will allow evaluation of response to ibrutinib 840 mg/day in patients with non-GCB DLBCL subtype.

2.5.4 In FL, MM or WM

- NCT01779791 (DAWN) is a single-arm, open-label phase II study in patients with chemo-immunotherapy-resistant FL that was initiated in February 2013.
- NCT01478581 is an open-label phase II study in patients with relapsed/refractory MM with interim results pertaining to disease markers (Sect. 2.1). Further results from this study are expected in 2014.
- NCT01614821 is an open-label phase II study in patients with relapsed/refractory WM with interim results (Sect. 2.3.4).

2.5.5 Phase IIIb Extension Study

- NCT01804686 is an open-label phase IIIb long-term extension study to evaluate the safety and efficacy of ibrutinib 560, 420, 280 or 140 mg/day in patients with CLL, SLL, MCL, FL and DLBCL who have had at least 6 months of ibrutinib treatment and who are continuing to benefit. The study will recruit ≈200 patients.

2.6 Companion Diagnostics

In 2011, Abbott received US FDA approval for its proprietary Vysis® CLL FISH Probe Kit. The test targets

multiple genes, including tumour protein 53 located on chromosome 17p, and is used to investigate the prognosis and to determine genetic marker status of CLL patients. Abbott is collaborating with Janssen and Pharmacyclics to develop a molecular companion diagnostic test to identify patients with CLL who are most likely to respond to treatment with ibrutinib [39]. The three companies are developing a FISH-based test to identify CLL patients with a chromosome 17p deletion, as patients with this deletion are poor responders to chemo-immunotherapy. Hence, the companion diagnostic will help to identify this specific population, which has a high unmet medical need. Clinical development is underway in the USA [39].

3 Current Status

Ibrutinib received its first approval in the US on 13 November 2013 for use the treatment of patients with MCL who have had at least one prior treatment [8, 40].

References

1. Lymphoma Research Foundation. Non-Hodgkin lymphoma (NHL). 2012. http://www.lymphoma.org. Accessed 9 Nov 2013.
2. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1922–2001. Blood. 2006;107(1):265–76.
3. Gaidano G, Foà R, Dalla-Favera R. Molecular pathogenesis of chronic lymphocytic leukemia. J Clin Invest. 2012;122(10):3432–8.
4. Murawski N, Pfreundschuh M. New drugs for aggressive B-cell and T-cell lymphomas. Lancet Oncol. 2010;11(11):1074–85.
5. Chang JE, Kahl BS. Current status of targeted therapies for mantle cell lymphoma. Drugs. 2011;71:2307–26.
6. Danilov AV. Targeted therapy in chronic lymphocytic leukemia: past, present, and future. Clin Ther. 2013;35(9):1258–70.
7. Wiestner A. Targeting B-cell receptor signaling for anticancer therapy: the Bruton's tyrosine kinase inhibitor ibrutinib induces impressive responses in B-cell malignancies. J Clin Oncol. 2013;31(1):128–30.
8. Pharmacyclics, Inc. Imbruvica™ (ibrutinib) capsules for oral use; US prescribing information. 2013. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf. Accessed 10 December 2013.
9. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol. 2013;31(1):88–94.
10. Pharmacyclics, Inc. New drug application filing for ibrutinib accepted in two B-cell malignancies by the U.S. FDA [media release]. Aug 29 2013. http://www.pharmacyclics.com.
11. Pharmacyclics, Inc. New drug application for ibrutinib submitted to the U.S. FDA [media release]. Jul 10 2013. http://www.pharmacyclics.com.
12. Celera Corp. Celera Corporation separates from Applera Corporation [media release]. Jul 1 2008. http://www.celera.com.
13. Pharmacyclics, Inc. Celera Genomics announces sale of therapeutic programs to Pharmacyclics [media release]. Apr 10 2006. http://www.pharmacyclics.com.
14. Celera Genomics. Celera Genomics reports first quarter fiscal 2006 results [media release]. Oct 27 2005. http://www.celera.com.
15. Quest Diagnostics Inc. Quest Diagnostics successfully completes acquisition of Celera [media release]. May 17 2011. http://www.questdiagnostics.com.
16. Pharmacyclics, Inc. Pharmacyclics announces collaboration with the National Cancer Institute to develop its novel Btk Inhibitor, PCI-32765 in hematologic malignancies [media release]. Aug 9 2011. http://www.pharmacyclics.com.
17. WuXi PharmaTech Inc. WuXi Pharma to partner with Pharmacyclics [media release]. Nov 15 2013. http://www.wuxiapptec.com.
18. Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood. 2013;122(15):2539–49.
19. Honigberg LA, Smith AM, Loury DJ. A clinical trial of the Bruton's tyrosine kinase inhibitor PCl-32765 in naturally occurring canine lymphoma [abstract no. 3740]. In: 100th Annual Meeting of the American Association for Cancer Research; Apr 18–22 2009; Denver.
20. Honigberg L, Smith A, Chen J, et al. PCL-31523: an irreversible inhibitor of Bruton's tyrosine kinase that disrupts B cell receptor signaling, is cytotoxic to B cell lymphomas, and is active in an animal arthritis model [abstract no. 5398]. In: 98th Annual Meeting of the American Association for Cancer Research; Apr 14–18 2007; Los Angeles.
21. Ponader S, Chen SS, Buggy JJ, et al. Bruton's tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing in vitro and in vivo. Blood. 2012;119:1182–9.
22. Nimbus Discovery. Nimbus Discovery IRAK4 inhibitors demonstrate synergistic effects with BTK iInhibitor ibrutinib [media release]. Dec 9 2012. http://www.nimbusdiscovery.com.
23. Elias L, Chen J, Buggy J. BTK inhibitor ibrutinib inhibits breast cancer growth by inhibiting ErbB2 kinase [abstract no. C258]. In: 25th AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; Oct 19–23 2013, Boston.
24. Lobe CG, Allain MJ, Yang W. Activity of BTK and HDAC inhibitors alone and in combination in a mouse model of non-small cell lung cancer [abstract no. C243]. In: 25th AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics; Oct 19–23 2013, Boston.
25. Vij R, Chang BY, Berdeja JG, et al. Early changes in cytokines, chemokines and indices of bone metabolism in a phase 2 study of the Bruton tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765) in patients with relapsed or relapsed/refractory multiple myeloma (MM) [abstract no. 653]. In: 54th Annual Meeting of the American Society of Hematology; Dec 8–11 2012, Atlanta.
26. Nathan F, Jeff S, Sonali S, et al. A phase I trial of BTK inhibitor PCI-32765 in patients with relapsed non-Hodgkin's lymphoma: evidence of antitumor activity [abstract no. 0893]. In: 15th Congress of the European Haematology Association; Jun 10–13 2010, Barcelona.
27. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507–16.
28. Wiestner A, Farooqui M, Valdez J, et al. Single agent ibrutinib (PCI-32765) is highly effective in chronic lymphocytic leukaemia patients with 17p deletion. Hematol Oncol. 2013;31:98.
29. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369(1):32–42.

30. Brown JR, Barrientos JC, Barr PM, et al. Ibrutinib in combination with bendamustine and rituximab is active and tolerable in patients with relapsed/refractory CLL/SLL: final results of a phase 1b study [abstract no. 525]. In: 55th Annual Meeting of the American Society of Hematology; Dec 7–10 2013; New Orleans.
31. Burger JA, Keating MJ, Wierda WG, et al. Efficacy and safety of ibrutinib in combination with rituximab in high-risk CLL patients. Hematol Oncol. 2013;31:193–4.
32. Burger JA, Keating MJ, Wierda WG, et al. Ibrutinib in combination with rituximab (iR) is well tolerated and induced a high rate of durable remissions in patients with high-risk chronic lymphocytic leukemia (CLL): new, updated results of a phase II trial in 40 patients [abstract no. 675]. In: 55th Annual Meeting of the American Society of Hematology; Dec 7–10 2013; New Orleans.
33. Farooqui M, Aue G, Valdez J, et al. Single agent ibrutinib (PCI-32765) achieves equally good and durable responses in chronic lymphocytic leukemia (CLL) patients with and without deletion 17p [abstract no. 673]. In: 55th Annual Meeting of the American Society of Hematology; Dec 7–10 2013; New Orleans.
34. O'Brien S, Furman RR, Fowler N, et al. The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765) monotherapy demonstrates long-term safety and durability of response in chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) patients in an open-label extension study [abstract no. 4163]. In: 55th Annual Meeting of the American Society of Hematology; Dec 7–10 2013; New Orleans.
35. Wilson WH, Gerecitano JF, Goy A, et al. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), has preferential activity in the ABC subtype of relapsed/refractory de novo diffuse large B-cell lymphoma (DLBCL): interim results of a multicenter, open-label, phase 2 study [abstract no. 686]. In: 54th Annual Meeting of the American Society of Hematology; Dec 8–11 2012, Atlanta.
36. deVos S, Wilson WH, Gerecitano JF, et al. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), has preferential activity in the activated B cell-like (ABC) subtype of relapsed/refractory (RR) DLBCL: interim phase 2 results [abstract no. S1180]. In: 18th Congress of the European Haematology Association; Jun 13–16 2013, Stockholm.
37. Treon S, Tripsas C, Yang G, et al. A prospective, multicentre, phase II study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed and refractory Waldenstrom's macroglobulinemia [abstract no. 067]. Hematol Oncol. 2013;31:119.
38. Treon SP, Tripsas K, Yang G, et al. A prospective multicenter study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenstrom's macroglobulimemia [abstract no. 251]. In: 55th Annual Meeting of the American Society of Hematology; Dec 7–10 2013, New Orleans.
39. Abbott, Inc. Abbott to collaborate with Janssen and Pharmacyclics on development of companion test for investigational leukemia therapy [media release]. Feb 21 2013. http://www.abbott.com.
40. US Food and Drug Administration. Imbruvica. 2013. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/205552Orig1s000ltr.pdf. Accessed 9 December 2013.