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Ibrutinib for the treatment of mantle cell lymphoma

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Mantle cell lymphoma (MCL) is a rare and aggressive form of non-Hodgkin's lymphoma. It can follow a heterogeneous clinical course but generally patients relapse early after standard immunochemotherapy regimens and develop resistance to subsequent therapies. For younger patients, intensive approaches followed by autologous stem cell transplantation offer excellent long-term disease control but with the possible exception of an allogenic stem cell transplant, MCL is an incurable condition. As MCL principally affects older individuals, the majority of patients are not candidates for such intensive approaches. Ibrutinib is an orally active, Bruton's tyrosine kinase inhibitor. It inhibits signaling pathways downstream of Bruton's tyrosine kinase that appear critical for the proliferation and survival of MCL. As a single agent it has shown extremely promising activity in relapsed and refractory MCL patients with an excellent side-effect profile. The exact role for ibrutinib in the treatment of MCL is yet to be established; however, it is likely to fundamentally change the way we treat this disease.

KᴇʏᴡᴏʀᴅS: Bruton's tyrosine kinase inhibitor • ibrutinib • mantle cell lymphoma

Mantle cell lymphoma (MCL) is a rare B-cell malignancy that accounts for 4–10% of non-Hodgkin's lymphoma (NHL). It is characterized by the t(11:14)(q13,q32) translocation that juxtaposes the proto-oncogene CCDN1, which encodes cyclin D1, at chromosome 11q13, to the immunoglobin heavy chain gene at chromosome 14q32 [1]. The incidence of MCL is approximately 1 per 100,000 population in Europe and the USA [2], with a median age at diagnosis around 65 years and a male predominance. It generally presents with an advanced stage and commonly involves the extra nodal sites particularly the bone marrow, gastrointestinal tract, liver and spleen [3].

MCL exhibits a heterogeneous clinical course with 10–30% of the patients presenting with clinically indolent disease [4–6]. The overall median survival is 4–5 years, but the patients with an indolent subtype can have a median survival of 5–12 years [6]. Almost all patients have a response to initial therapy, however, complete responses occur in fewer than 50% of patients and responses are usually shorter than 2 years. The median duration of remission in most trials is 1.5–3 years and median survival is 3–6 years with standard chemotherapy [7]. Younger patients (<65 years) benefit from a more intensive treatment approach, which incorporates rituximab and high-dose cytarabine combination chemotherapy followed by an autologous stem cell transplant [3,7–9]. However, given that the median age of MCL at diagnosis is 65 years, a significant proportion of patients are not suitable for the intensive treatment regimens.

There is currently no widely accepted standard therapy for patients following relapse and second responses are often poor. There is a clear unmet need to improve treatment for these patients. With the continued advancement in the understanding of the pathogenesis of MCL and other B-cell malignancies, potential targets for therapeutic intervention are evolving and drugs are being developed to target them [1,10–12]. One of the most exciting novel agents is ibrutinib (PCI-32765), an inhibitor of Bruton's tyrosine kinase (BTK).

BTK structure, function & signaling in MCL

BTK is expressed in all hematopoietic lineages with the exception of T cells and plasma cells, but is particularly critical for the development, survival and function of B lymphocytes [13–15]. In 1952, Ogden Bruton, an American army pediatrician, described a condition in boys, which was manifested by an absence of gamma globulins and recurrent bacterial infections, now known as X-linked agammaglobulinemia
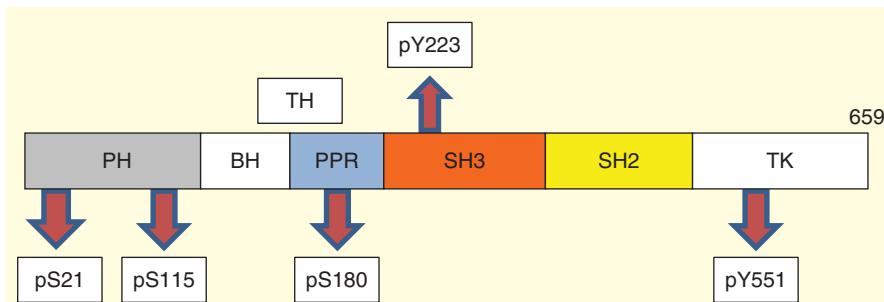
Figure 1. Schematic representation of Bruton's tyrosine kinase domains and regulatory phosphorylation sites (indicated by arrows).
BH: BTK homology region; PH: Pleckstrin homology; Phosphoserines: pS21, pS115, pS180; Phosphotyrosines: pY223 and pY551; PPR: Polyproline region; SH2: Src-homology 2; SH3: Src-homology-3; TH: Tec homology; TK: Tyrosine kinase domain.

(XLA) [16]. XLA is a rare X-linked genetic disorder affecting young male children. It is usually diagnosed in children older than 6 months, who present with recurrent infections and are found to have a total or almost total absence of B lymphocytes and plasma cells together with low immunoglobulin levels. This condition has been shown to be caused by mutations within the BTK gene that resulted in a block in B-cell maturation and failure of immunoglobulin production. It is perhaps unsurprising that pharmacological inhibition of BTK has activity against neoplastic B lymphocytes, it is more surprising though that pharmacological inhibition of BTK has low levels of toxicity and does not replicate the clinical picture of XLA.

BTK itself is a member of the TEC family of non-receptor tyrosine kinases and its structure is characterized by five domains (pleckstrin homology, TEC homology, SRC homology 3, SRC homology 2 and tyrosine kinase) (FIGURE1) [13–15,17]. It is a key signal protein lying downstream of the B-cell receptor (BCR) [11,18], where it is recognized to be activated by BCR-linked signal molecules such as LYN and SYK [17,19,20]. BTK is also activated by other important signals encountered by B lymphocytes, including growth factors, chemokines, cytokines, integrins and Toll-like receptors placing it at a key point in the control of signals between the B lymphocyte and its microenvironment. BTK is found principally within the cytoplasm, but translocates to the plasma membrane for activation. This process is mediated through binding of phosphatidylinositol-3,4,5-trisphosphate generated through the conversion of membrane-bound phosphatidylinositol 4,5-biphosphate by phosphatidylinositol-3-kinase to the pleckstrin homology domain of BTK [13,21,22]. Phosphorylation at tyrosine 551 within the kinase domain leads to a conformational change enabling autophosphorylation at tyrosine 221 within the TEC homology domain and full activation. Activated BTK phosphorylates phospholipase Cγ2, generating secondary messengers that activate PKCβ [22], triggering calcium mobilization and initiating the activation of other signaling molecules that include MAP kinases and NF-κB (via phosphorylation of IκB kinase-IKK to activated NF-κB) [11,18]. These signal processes are critical for the regulation of apoptosis, promotion of cell survival and further B-cell development (FIGURE 2) [11,23].

Why MCL should be particularly sensitive to BTK inhibition is unclear. The neoplastic lymphocytes of MCL have a characteristic aberrant expression of cyclin D1, this overexpression is believed to drive inappropriate cell cycle progression [1]. The effectiveness in MCL of drugs that inhibit BTK emphasizes the additional importance of signal pathway activation in the pathogenesis of MCL [24,25]. In this regard, although MCL was originally thought to resemble a pre-germinal center, naïve lymphocyte, MCL has been shown to have somatic mutations in the variable region of the immunoglobulin heavy chain gene in up to 40% of cases indicating exposure to antigen and a germinal/post-germinal center phenotype [10,26–28]. In other cell types, this phenotype is associated with ongoing dependence on BCR signals and a profound dependence on signals from the tissue microenvironment. In this regard, proteomic analysis has demonstrated that phosphoproteins of the BCR signaling pathway are abundantly expressed in MCL cell lines, and the BCR-linked PI3K/AKT pathway has been implicated in the pathogenesis of MCL [21,25,29]. Understanding of this process is an active area for research that may open new therapeutic approaches.

Development of ibrutinib & the pharmacology

Ibrutinib, $C_{25}H_{24}N_6O_2$, (1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazole[3,4-d]pyrimidin-1-y]piperidin-1-yl}prop-2-en-1-one) [19] is an orally administered selective small molecule (lose and irreversible) small molecule inhibitor of BTK, which irreversibly binds to the cysteine Cys-481 residue at the active site of BTK inhibiting Tyr-223 auto-phosphorylation.

Originally, ibrutinib or PCI-32765 was developed by Celera and later by Pharmacyclics as a targeted therapy for rheumatoid arthritis [19,30] and subsequently lymphoma. In, in vitro cell assays, it inhibited phosphorylation of BTK at very low concentrations (IC$_{50}$, 0.5 nm) in B-cell lymphoma cell lines and inhibited the ability of primary B cells to be activated after stimulation at the BCR [19]. The first in vivo dosing of ibrutinib in canines with naturally occurring B-cell lymphoma saw an objective response rate of 38% [30].

After oral administration the drug is both absorbed and eliminated rapidly (peak concentration 1–2 h after absorption, terminal half life 4–8 h). There is no accumulation of ibrutinib even following repeated dosing. Patients over 65 years of age have a 30% increase in plasma concentration, but this has not translated into increased toxicity [24]. It is metabolized by CYP450 enzyme 3A and therefore co-administration with CYP3A4/5 strong inhibitors should be avoided [31,32].

Using fluorescent-probe technology, BTK site occupancy by ibrutinib was assessed in the Phase I study [24]. This was demonstrated to be greater than 95% in all patients with doses as low as 2.5 mg/kg/day [24,31]. The BTK site occupancy was
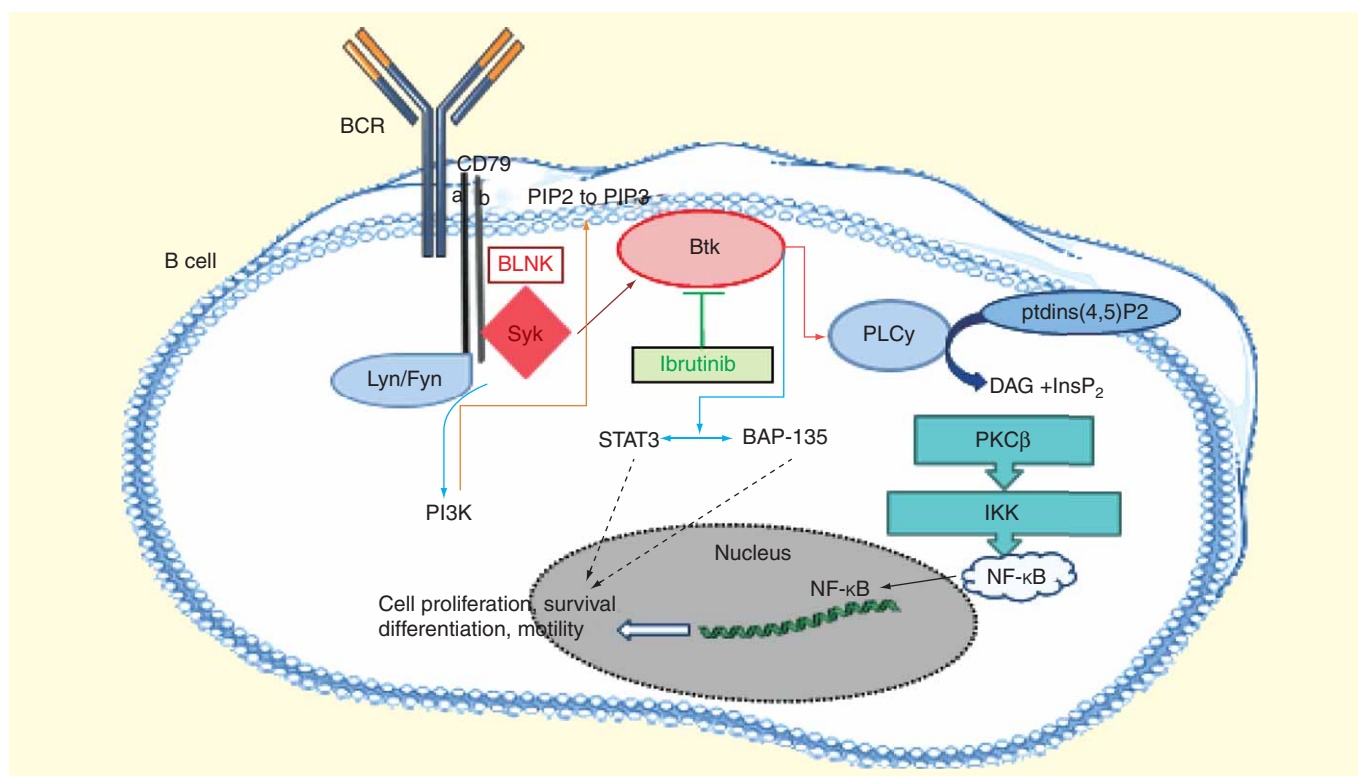
Figure 2. A simplified B-cell receptor signaling pathway. The BCR is activated as an antigen is attached, initiating the phosphorylation of CD79a and CD79b (within the cytoplasmic tails of their ITAMs), by the tyrosine kinases Lyn and Fyn. BTK, BLNK, PI3K among others are recruited to the membrane and Syk in turn is recruited and phosphorylates BTK and multiple other substrates including PI3K. Phosphorylated BTK activates signals downstream to induce activation of NF-κB, which is involved in B-cell proliferation and survival. BTK also activates other molecules, which are involved in B-cell survival and proliferation. The irreversible inhibition of BTK by ibrutinib stops the BTK's downstream cascade of signals, which in turn inhibits or affects B-cell proliferation, motility, differentiation and survival.
BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; ITAMs: Immunoreceptor tyrosine kinase activation motifs.

maintained for 24 h despite rapid drug clearance as indicated by BTK probe intensity reduction from 100% to normal within 4 h. This demonstrated a prolonged pharmacodynamic effect and permitted once-a-day dosing. Interestingly, no reduction in serum immunoglobin levels was observed, even in patients treated with more than 12 cycles, which one might have anticipated based on clinical findings observed in XLA.

Efficacy
The Phase I study
The Phase I study with ibrutinib included patients with relapsed/refractory B-cell lymphoma and chronic lymphocytic leukemia (CLL) [24,30]. Two schedules were evaluated: one treated daily for 28 days followed by 7 days rest period, the other dosed continuously. Fifty-six patients with a median age of 65 years (range: 41–82) were treated over 7 escalating dose cohorts. Dose-limiting events were not observed despite escalation to a dose of 12.5 mg/kg/day. By using a fluorescent affinity probe it was possible to determine the occupancy of the BTK binding site by ibrutinib. Full occupancy occurred at a dose of 2.5 mg/kg/day. Fifty-six patients were recruited to the trial, nine (16%) had relapsed/refractory MCL. Fifty out of fifty-six patients were evaluable and the objective overall

response rate (ORR) and complete response (CR) was 60 and 16%, respectively. Patients with MCL had the highest response rate (78% [7/9]), with 3 patients achieving CR.

A fixed continuous dosing of 560 mg/day achieved full BTK active occupancy in a range of individual body weights and this dose was adapted for subsequent study in NHL patients. A lower dose of 420 mg/day was chosen for patients with CLL.

Phase I: safety & tolerability
Within the Phase I trial only two dose-limiting toxicity events were observed: an allergic hypersensitivity reaction (which occurred in a patient prone to hypersensitivity reactions) and a case of neutropenia. The most common adverse events were grade I or II in severity affecting about 10% of the patients in each cohort. The adverse events included diarrhea, nausea or vomiting, decreased appetite or dyspepsia, fatigue, myalgia, cough and edema, which were usually self-limiting. The grade III or IV adverse events were infrequent and independent of dose. Grade III or IV hematological toxicity included neutropenia (12.5%), thrombocytopenia (7.2%) and anemia (7.1%), with no cumulative toxicity observed. Subsequent and later adverse events with continued therapy included grade IV pain

Table 1. Summary of Phase I and II trials.

Trials with MCL and ibrutinib	Patients (n) with MCL	ORR (%)	CR/PR (%)	PFS months	Ref.
Phase I trial ibrutinib has significant activity in patients with relapsed/refractory B-cell malignancy	9	78	33	n/a	[24]
Phase II trial targeting Btk with ibrutinib in relapsed/ refractory MCL	111	68	21/47	13.9	[33]

CR: Complete response; MCL: Mantle cell lymphoma; n/a: Not available; ORR: Overall response rate; PFS: Progression-free survival; PR: Partial response.

and cerebrovascular accident, grade III small bowel obstruction and a flare of chronic obstructive airway disease.

The Phase II study

As a consequence of the encouraging results observed in the Phase I study in patients with MCL, a non-randomized, multi-center Phase II, open-label trial was undertaken (TABLE 1) [33]. This study recruited 111 patients with relapsed/refractory MCL. Treatment was with continuous dose of ibrutinib of 560 mg/day. The median age was 68 years (range: 40–84) and the median number of prior therapies received was 3 (range 1–5; 55% received greater than 3 prior therapies). Overall, 77% of the patients had stage IV disease. Eighty-six percent of the patients had either intermediate (38%) or high-risk disease (49%), according to the simplified Modified International Prognostic Index (sMIPI). Eighty-nine percent of the patients had prior exposure to therapy containing rituximab. While not a randomization within a trial, patients were classified into two groups: patients with and without prior exposure to bortezomib (n = 48 vs 63, respectively).

The ORR for all patients was 68%, with 47 and 21% achieving partial response (PR) and CR, respectively. The response rates were similar among patients who previously had bortezomib therapy and those who did not. The median duration of response was 17.5 months (range: 0–19.6) and the median time to response was 1.9 months (range: 1.4–13.7). The median progression-free survival was 13.9 months in all treated patients. At the time of analysis, the estimated overall survival rate was 58% at 18 months. The response to ibrutinib appeared independent of baseline characteristics or the presence of risk factors associated with treatment failure with chemotherapy, this includes bulky disease, blastoid histology, high MIPI and prior transplantation. The quality of remission seen on treatment improved with ongoing exposure with some patients taking up to 9 months to achieve PR.

The Phase II study: safety & tolerability

The safety data published were similar to that observed in the Phase I study. The majority of the adverse events observed were grade I or II in nature. The most common non-hematological adverse events occurring in more than 20% of the patients included diarrhea (50%), fatigue (41%), nausea (31%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper respiratory tract infection (23%), vomiting

(23%) and decreased appetite (21%). Pneumonia was the most common infection. Fewer than 19% of the patients experienced grade I or II hematological adverse events.

Grade III and IV adverse events were uncommon. Significant hematological adverse events included neutropenia (in 16% of patients), thrombocytopenia (in 11%) and anemia (in 10%). In common with the Phase I trial, no change to the serum immunoglobulin levels was evident. Seven percent of the patients had to stop the drug due to adverse events, which included myocardial infarction, sepsis/ infection, disease progression and subdural hematoma.

Grade III bleeding occurred in five patients (two subdural hematoma, two hematuria and one gastrointestinal hemorrhage). Four patients had subdural hematoma, which were all associated with falls, head trauma or both. Notably, all the patients with subdural hematoma had received either aspirin or warfarin. Consequently, it was advised to avoid co-administration of antiplatelet or anticoagulation while on ibrutinib, especially warfarin [32]. The bleeding propensity may be secondary to a platelet function defect. Farooqui et al., presented data on the platelet function of three patients with CLL who had received ibrutinib. There was a prolongation of epinephrine closure times on day 2 and by day 28, this had resolved with continued treatment in two patients and improved in one patient. All closure times by ADP were low or normal. No patients with abnormal results on platelet function analyzer had spontaneous ecchymosis. The mildly elevated levels of von Willebrand factor and factor VIII normalized at day 28. This preliminary report concluded no significant effect by ibrutinib on platelet function [34].

An interesting finding from the Phase II trial was the substantial rise in circulating MCL cells in the peripheral blood following therapy. This usually occurred 10 days after commencement of therapy and peaked at a median time of 4 weeks. Thirty-eight percent of the patients had this transient increase of greater than 50% from baseline. The elevated lymphocyte count decreased toward the end of the second cycle and diminished during cycle 4 or 5. These lymphocytes were CD19^{+} CD5^{+} CD3^{−} and light chain restricted confirming them to be circulating MCL cells. A recent study by Chang et al. [35] evaluated this phenomena. They demonstrated the expression of CXCR4 on the circulating MCL cells and inhibition by ibrutinib of downstream signaling from receptors for stromal adhesion, CXCL12 and

Table 2. Ongoing trials with ibrutinib in mantle cell lymphoma patients.

Trial	Phase	Description of trial	Target patient number	Primary outcome	Ref.
Current trials with ibrutinib in MCL[†]					
'RAY' active, not recruiting	III	For relapsed/refractory MCL patients who have had a least one prior rituximab containing therapy ibrutinib daily vs temsirolimus	280	PFS	[58]
'SHINE' Active and recruiting	III	Randomized, double-blind, placebo study of ibrutinib in combination with bendamustine and rituximab for newly diagnosed patients with MCL over the age of 65 years. Multi-center trial. Ibrutinib + bendamustine + rituximab vs placebo + bendamustine + rituximab – 1:1 randomization	560	PFS	[39]
Active, not recruiting	I	A Phase I, dose-escalation trial of rituximab and bendamustine in combination with Bruton's tyrosine kinase inhibitor, PCI-32765, in patients with relapsed diffuse large B-cell lymphoma, mantle cell lymphoma or indolent non-Hodgkin's lymphoma. Hypothesis that ibrutinib in combination with rituximab and bendamustine will kill more tumor cells	48	MTD	[64]
Active, not recruiting	IIIb	A Phase IIIb, multicenter, open-label, PCI-32765 (ibrutinib) long-term extension study. This is an open-label (identity of assigned study drug will be known) study designed to collect long-term safety and efficacy data and provide PCI-32765 (ibrutinib) access to participants in completed PCI-32765 studies	n/a	ORR	[65]
Active, not recruiting	II	A Phase II study of ibrutinib plus rituximab in patients with relapsed/refractory mantle cell lymphoma. The goal of this clinical research study is to learn if a combination of ibrutinib and rituximab can help control relapsed/refractory MCL. The safety of this drug combination will also be studied	50	ORR	[66]
Active, recruiting	II	A multi-center Phase II study with safety run-in evaluating the efficacy and safety of ublituximab in combination with ibrutinib in patients with select B-cell malignancies. The purpose of this study is to evaluate the safety and effectiveness of ublituximab in combination with ibrutinib in patients with advanced hematologic malignancies. Relapsed/refractory MCL patients	60	Safety of ublituximab with ibrutinib	[67]
Active and recruiting	I	A Phase I study of ibrutinib (PCI-32765) in combination with lenalidomide in relapsed and refractory B-cell non-Hodgkin's lymphoma. This Phase I trial studies the side effects and best dose of lenalidomide and ibrutinib in treating patients with relapsed/refractory B-cell non-Hodgkin's lymphoma. Biological therapies, such as lenalidomide, may stimulate the immune system in different ways and stop cancer cells from growing. Ibrutinib may stop the growth of cancer cells by blocking some of the enzymes needed for cell growth. Giving lenalidomide with ibrutinib may be an effective treatment for non-Hodgkin's lymphoma	34	DLT and MTD and toxicity	[68]

[†]Status of trials indicated was according to their individual status in July 2014.
DLT: Dose-limiting toxicity; MTD: Maximum tolerated dose; n/a: Not available; PFS: Progression-free survival.

CXCL13. The cells with decreased CXCR4 levels have impaired chemotaxis, which helps explain the re-distribution observed between the tissue compartment and the peripheral blood.

In conclusion, ibrutinib has shown durable and impressive single agent activity, with a modest side-effect profile. The responses observed appear durable and are seen in all risk groups [33]. As a consequence, ibrutinib (Imbruvica™) has been recently approved by the US FDA through the FDA's Breakthrough Therapy Designation Pathway [36].

Trials involving ibrutinib & ibrutinib in combination with chemoimmunotherapy

The impressive response rates observed in relapsed/refractory MCL patients have led to the initiation of further trials both as a single agent and in combination with chemotherapy (TABLE 2). The modest side-effect profile and apparent lack of hematological toxicity lends itself to combining ibrutinib with the conventional chemotherapeutic approaches for MCL.

Early results of a Phase I study involving ibrutinib in combination with bendamustine and rituximab have been reported in

Table 3. Bruton's tyrosine kinase inhibitors currently in preclinical or clinical development.

BTK inhibitors molecule	Reversible or irreversible	BTK-specific and BTK IC_{50}	Current development phase	Comments	Ref.
Ibrutinib (Imbruvica™)	Irreversible	Broad – includes other kinases and 0.5 nmol/l	Phase II and III clinical trials	See text – US FDA licensed in the USA for relapsed/refractory MCL	[14,33]
ONO-4059	Reversible	Specific and 2.2 nmol/l	Phase I clinical study	Early results presented at the ASH 2013, currently Phase I trial ongoing	[47]
CC-292	Irreversible	Specific and <0.5 nmol/l	Phase II clinical trial	High specific for BTK, and currently clinical trial ongoing	[50]
LFM-A13	Reversible	Non-specific includes other kinases and 2.5 µm	Preclinical	Inhibits Janus 2 kinases as well as BTK and other kinases. No clinical study data available at present	[54]
HM-71224	NK	Highly selective and NK	Phase I clinical trial in normal subjects	See text	[42]
GDC-0843	Reversible	NK and 5.9 nmol/l	Phase I clinical trial in normal subjects	See text and developed by CGI Pharma Genentech	[42]

ASH: American Society of Hematology; BTK: Bruton's tyrosine kinase; MCL: Mantle cell lymphoma; NK: Not known.

abstract form [37]. Patients with CD20⁺ NHL were treated with standard rituximab 375 mg/m² day 1, bendmustine 90 mg/m² days 1 and 2 and ibrutinib at either 280 or 560 mg given daily for 28 days repeated for 6 cycles. After 6 cycles, ibrutinib alone was continued in responding patients. Eleven patients with relapsed/refractory NHL were enrolled with a median age of 72 (range: 45–84). Newly diagnosed MCL patients not suitable for an autologous stem cell transplant were also eligible for this study. Three patients with MCL were among the 11 patients enrolled and all responded (2 CR and 1 PR). The most common side effect was severe lymphopenia that was observed in 64% of patients, which was similar to the grade 3 and 4 lymphopenia (74%) reported by Rummel et al., in the Phase III trial comparing frontline rituximab and bendamustine versus rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in MCL and indolent NHL [38]. This did not translate into any significant infection (>grade 3) or prove a dose-limiting toxicity. This report concluded the combination of ibrutinib with bendamustine and rituximab was well tolerated and demonstrated good activity in previously untreated and relapsed MCL. Follow on from this, the 'SHINE' trial is assessing ibrutinib in combination with bendamustine and rituximab in a randomized double-blind design as frontline therapy [39].

A Phase Ib study has evaluated the feasibility of ibrutinib with R-CHOP [40,41]. This study gave ibrutinib to CD20⁺ NHL which included MCL. The dose of ibrutinib administered was 280, 420 and 560 mg daily in combination with

standard R-CHOP. Seventeen patients were enrolled. The most common side effect was neutropenia (77%); however, R-CHOP did not alter ibrutinib pharmacokinetics and ibrutinib did not alter vincristine pharmacokinetics.

Ibrutinib has also demonstrated good clinical efficacy with limited toxicity as a single agent drug in the treatment of other NHL histological subtypes as described above. There are currently several trials underway with ibrutinib in combination and as a single agent as shown in TABLE 2.

Other BTK inhibitors

There are a number of compounds with BTK inhibitory properties that are at varying stages of development including CC-292, ONO-4059, LFM-A13, GCD-0834 and HM-71224 among others (TABLE 3) [42,43].

ONO-4059 (ONO-WG-307) (ONO Pharmaceutical Co. Osaka, Japan) is an orally active, reversible inhibitor of BTK that binds to Cys-481 and acts by blocking the autophosphorylation at position Y223 in the BTK SRC homology 3 domain [44]. Preclinical studies have demonstrated suppression of Akt-mediated signaling and cellular protein kinase D activity [45]. ONO-4059 showed good preclinical activity in B-cell malignancies [46] and subsequently early Phase I results of ONO-4059 in relapsed B-cell lymphoma were presented at the American Society of Hematology Annual Meeting 2013. Twenty-two patients were evaluated for efficacy and seven of these patients had relapsed/refractory MCL. The best ORR at the time of presentation in the multiply relapsed/refractory

MCL patients was 43% (3/7). The best overall response (75% [6/8]) was observed in diffuse large B-cell lymphoma [47]. This study has shown promising results in relapsed/refractory B-cell NHL patients treated with single agent ONO-4059 and the study is currently ongoing. ONO-4059 has also shown impressive response rates in CLL [48].

CC-292 (formerly known as AVL-292) (Celgene Corp., Summit, NJ, USA) is an orally available, irreversible small molecule inhibitor of BTK. CC-292 binds with Cys-481 and has a high specificity for BTK compared with other SRC family kinases. CC-292 was evaluated in healthy adult subjects and was safe and well tolerated at dose levels ranging from 0.5 to 7.0 mg/kg [49]. BTK occupancy was greater than 84% and the half-life was 1.9 h with a sustained occupancy over a 24 h period. Given these results, CC-292 was entered in a Phase Ib study and early results were reported on 12 patients with relapsed/refractory B-cell NHL (8 CLL, 1 diffuse large B-cell lymphoma, 1 follicular lymphoma, 2 marginal zone lymphoma) [50]. Doses of CC-292 evaluated were 125, 250 and 400 mg on a continuous 28-day cycle. CC-292 was well tolerated from 125 to 400 mg and early efficacy analysis showed 10/11 patients with stable disease. The full BTK occupancy was achieved at >250 mg daily dose (q.d.). More updated results on 86 patients with B-cell malignancy was reported by Brown *et al.*, 2013. Seventeen efficacy-evaluable B-cell NHL patients demonstrated stable disease and the median duration of treatment was 176 days (range: 16–473). The ORR was 31% at 750 mg q.d., 50 and 66.7% at 1000 mg q.d. and 375 mg twice daily, respectively. Of the 50 CLL patients, 34% (17/50) showed a partial remission and 45% (24/50) showed lymph node reduction. Dose-limiting toxicity was observed in three patients with pneumonitis, thrombocytopenia and altered mental state. Common adverse effects were diarrhea, fatigue, muscle spasm and headaches. There are no data published yet on patients with MCL treated with CC-292. Currently, there is an ongoing study with CC-292 in combination with lenalidomide in relapsed/refractory B-cell NHL [51].

LFM-A13 (University of Southern California, Los Angeles, CA, USA) is a novel, dual BTK/polo-like kinase inhibitor with antiproliferative, pro-apoptotic and chemosensitizing effects in leukemia/lymphoma and breast cancer cells [52,53]. It binds to the catalytic site of Btk and is highly selective of BTK. LKM-A13 has demonstrated sensitization of the human Philadelphia positive acute lymphoblastic leukemia-1 and NALM-6 pre-B ALL cell lines to ceramide- and vincristine-induced apoptosis [54]. As yet, there are no clinical data published for LFM-A13, but this molecule has potential in chemoresistance B-cell malignancy.

HM-71224 (Hanmi Pharmaceuticals, Seoul, Korea) is an oral small molecule BTK inhibitor, which has progressed into Phase I clinical trials. Its pharmacodynamics, PK, safety and tolerability is to be assessed in healthy volunteers in Korea and the Netherlands [42,55].

GDC-0834, RN-486, CGI-560, CGI-1746 are all small molecule inhibitors of BTK, which are under development,

primarily for inflammatory disease, but these molecules also have the potential to be used for the treatment of B-cell malignancy. The available clinical data for the other BTK inhibitors mentioned are extremely preliminary and as such any direct comparisons with ibrutinib are not really possible.

Conclusion

The approval by the FDA of ibrutinib is a potential milestone for the treatment of MCL in patients with relapsed/refractory MCL. The overall response results reported by Wang *et al.* [33] for patients with relapsed/refractory MCL are so far the best reported results for a single agent in this disease. In addition, this agent exhibits an excellent side-effect profile including modest hematological toxicity that allows for its incorporation into standard chemotherapy regimens used in this disease. It is, as yet, not clear as to where ibrutinib best fits in the treatment algorithm for MCL, but it is likely to prove active at all stages of the illness. As trials progress, it is likely to rapidly become established as a cornerstone of therapy in this difficult disease.

Expert commentary

Of the B-cell lymphoproliferative disorders, MCL has one of the worst long-term outcomes. Remissions achieved with conventional chemotherapy are often short lived and incomplete. For younger patients, intensive cytarabine-based therapy followed by autologous stem cell transplantation has been a significant advancement but is not curative and given that the median age of MCL at diagnosis is 65 years is only applicable to a minority of patients.

The FDA approved the use of ibrutinib in relapsed/refractory MCL patients based on the results of the Phase II trial reported by Wang *et al.* [33]. This study demonstrated an ORR and CR of 68 and 21%, respectively with a median duration of response of 17.5 months. These results compare favorably with bortezomib (PINNACLE study [56]), lenalidomide (EMERGE study [57]) and temsirolimus (OPTIMAL study [56]), which are the only other licensed drugs in this disease. The ORR and CR for bortezomib observed in the PINNACLE study was 32 and 8%, respectively with duration of response of 9 months. The OPTIMAL study demonstrated ORR and CR of temsirolimus as 22 and 2% with duration of response of 4–7 months. Lenalidomide in the EMERGE study demonstrated an ORR and CR of 26 and 7%, respectively with a median duration of response of 16.6 months. In addition, ibrutinib shows better response rates when compared with the other single agents such as rituximab, flavopiridol and everolimus as shown in Table 4. Ibrutinib is the most active single agent yet seen and produces responses in all clinical situations including refractory disease, post-transplantation, high MIPI and blastoid variant cases.

The awaited results of the current ongoing Phase III trial, 'RAY', evaluating ibrutinib versus temsirolimus, will be the first head-to-head trial [58].

In addition to its efficacy, ibrutinib exhibits an excellent side-effect profile and the apparent lack of additional toxicity

Table 4. Single agents used in mantle cell lymphoma.

Study (year)	Agent	Phase	MCL patients selection	Patients (n)	ORR %	CR %	DOR (months)	Ref.
Wang et al. (2013)	Ibrutinib	II	R/R	111	68	21	17.5	[33]
PINNACLE	Bortezomib	II	R/R	155	33	8	9.2	[69]
OPTIMAL	Temsirolimus	III	R/R	162	22	2	7	[56]
Kouroukis et al. (2003)	Flavoparidol	II	37% untreated 63% R/R	30	11	0	3	[70]
Renner et al. (2012)	Everolimus	II	R/R	35	20	6	n/a	[71]
Witzig et al. (2011)	Everolimus	II	R/R	19	32	11	n/a	[72]
EMERGE	Lenalidomide	II	R/R	134	28	7.5	16.6	[57]
Eve et al. (2012)	Lenalidomide	II	R/R	26	31	8	22	[73]
Ghielmini et al. (2005)	Rituximab	II	R/R	54	28	2	15	[74]

CR: Complete response; DOR: Duration of response; n/a: Not available; n.r.: Not reported; ORR: Overall response rate; R/R: Relapsed/refractory.

observed to date when used in combination suggests it could be incorporated into all of the currently adopted active regimens. Ultimately, the question will be whether ibrutinib by itself or within a 'chemotherapy-free' regimen can be used in place of conventional chemotherapy. For more elderly patients where immunochemotherapy has significant toxic effects, the need for such an approach is more pressing. For the younger patients, adding ibrutinib to cytarabine-based therapy may deepen remission to such a point that it may obviate the requirement for an autologous stem cell transplant.

It seems likely that over the next couple of years the treatment paradigm for MCL will fundamentally change as the evidence base for ibrutinib grows. It has the potential to fundamentally change the way we approach this disease and holds the very real possibility that it could be used in place of chemotherapy. With a host of BTK inhibitors being developed and with other orally active targeted therapies that affect different cell survival pathways moving into clinical trials, rationale combinations studies will follow. It is likely that over the next couple of years we will see a fundamental shift in the approach to the management of this difficult disease.

Five-year view

The exact role of ibrutinib within the treatment algorithm for MCL is yet to be established. In the first place, ibrutinib will be combined with all of the common immunochemotherapy regimens that have demonstrable activity in MCL. In addition, combinations with other non-chemotherapeutic agents that have proven activity will be trialed. It is likely that this agent will feature in the treatment algorithm for elderly and frail patients first, as this is the cohort of patients who fail to tolerate many of the standard chemotherapy regimens. The tolerability of ibrutinib and its modest hematological side-effect profile mean it could be given to patients with significant co-morbidities, including myelosuppression, which can be a

problem at relapse for older patients. In some patients who are deemed unfit for standard chemoimmunotherapy, ibrutinib will be used as a single agent. A recent Phase Ib/II study in elderly untreated patients (median age 71 years [range: 65–84]) with CLL reported by O'Brien et al. [59] has demonstrated favorable safety and activity of ibrutinib utilized as monotherapy in this cohort of patients. Thirty-one patients (29 with CLL and 2 with small lymphocytic lymphoma) were enrolled and the objective response was 71% (22/31) and 13% (4/31) achieved CR with 55% (17/31) achieving PR. Toxicity was mainly grade I or II, which included diarrhea, nausea and fatigue. Three patients had grade III infection and one patient developed grade III neutropenia [59]. These results are encouraging and we would expect similar outcomes in elderly patients with MCL.

Young and fit patients with aggressive MCL should be considered for high-intensity therapy and stem cell transplantation [3,7]. This approach currently provides excellent long-term OS (80–96%) and PFS (of up to 72% at 3 years) [9,60,61]. However, this is not a curative therapy. In an attempt to improve on these results, the use of ibrutinib may deepen remissions to a point where consolidation is not required and conceivably could form part of maintenance after this high-intensity therapy. In addition, allogeneic transplantation is often considered following relapse after autologous transplantation. Ibrutinib could be used as re-induction for these patients where its lack of significant toxicity makes this an attractive option. It would also only need to be given for a short period of time, which removes affordability as an issue.

It is increasingly recognized that approximately 10–30% of the patients have clinically indolent behaving MCL [4–6]. These patients can be monitored without treatment and without adversely affecting the OS. If we can accurately identify this group of patients, a less intensive therapeutic approach such as single agent ibrutinib may well be sensible.

There is potential for the development of resistance to ibrutinib in MCL. There are several signaling pathways that contribute to the MCL pathogenesis, which include activated PI3K, Akt, WNT, Hedgehog and NF-κB, which promote tumor survival and proliferation [62]. These pathways offer escape mechanisms to ibrutinib's inhibitory action on BTK and mutations of BTK have been seen in patients with CLL [63]. These are only just emerging but an understanding of the interdependence of these pathways will lead to rational combinations of drugs being trialed that may prevent its emergence and possibly produce very durable remissions.

The final factor for this drug is the cost. The cost of ibrutinib is approximately US$132,000 per year [32]. While this is in line with a number of the newer orally active anticancer agents, it will inevitably affect its availability within some healthcare environments. This is not a challenge unique to ibrutinib, but as this is a very important advance in therapy it would be unfortunate if cost limited availability.

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Key issues

- Ibrutinib is a novel small molecule, which is orally active, irreversible inhibitor of Bruton's tyrosine kinase that binds on the Cys-481.
- It has been granted one of the first approvals through the US FDA's Breakthrough Therapy Designation Pathway.
- Ibrutinib is approved for use in relapsed/refractory mantle cell lymphoma patients who have had at least one prior therapy.
- The approval was granted following the Phase II trial, which demonstrated excellent single agent efficacy together with very modest toxicity in relapsed/refractory mantle cell patients.
- Ibrutinib's favorable toxicity profile potentially allows for it to be incorporated into existing chemotherapy regimens without problems.
- There are currently multiple studies ongoing to evaluate ibrutinib in combination with other immunochemotherapies.
- A number of Bruton's tyrosine kinase inhibitors are in early clinical development and multiple other small molecules with activity in mantle cell lymphoma are emerging.
- Ibrutinib is set to fundamentally change the treatment approach in mantle cell lymphoma.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Jares P, Colomer D, Campo E. Molecular pathogenesis of mantle cell lymphoma. J Clin Invest 2012;122(10):3416-23

2. Zhou Y, Wang H, Fang W. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer 2008;113(4):791-8

3. McKay P, Leach M, Jackson R, et al. Guidelines for the investigation and management of mantle cell lymphoma. Br J Haematol 2012;159(4):405-26

• Recommended references for further reading.

4. Eve H, Furtado M, Hamon M, Rule S. Time to treatment does not influence overall survival in newly diagnosed mantle-cell lymphoma. J Clin Oncol 2009; 27(32):189-90

5. Hsi ED, Martin P. Indolent mantle cell lymphoma. Leuk Lymphoma 2013;55(4): 761-7

6. Martin P, Chadburn A, Christos P. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009; 27(8):1209-13

7. Vose JM. Mantle cell lymphoma: 2013 Update on diagnosis, risk-stratification, and clinical management. Am J Hematol 2013;88(12):1082-8

8. Merli F, Luminari S, Ilariucci F, et al. Rituximab plus HyperCVAD alternating with high dose cytarabine and methotrexate for the initial treatment of patients with mantle cell lymphoma, a multicentre trial from Gruppo Italiano Studio Linfomi. Br J Haematol 2012;156(3):346-53

9. Geisler CH, Kolstad A, Laurell A, et al. Nordic MCL2 trial update: six-year follow-up after intensive immunochemotherapy for untreated mantle cell lymphoma followed by BEAM or BEAC + autologous stem-cell support: still very long survival but late relapses do occur. Br J Haematol 2012; 158(3):355-62

10. Navarro A, Clot G, Royo C, et al. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11 expression have distinct biologic and clinical features. Cancer Res 2012; 72(20):5307-16

11. Rickert R. New insights into pre-BCR and BCR signalling with relevance to C cell malignancies. Nature 2013;13(8):578-91

• Recommended references for further reading.

12. Brett LK, Williams ME. Current and emerging therapies in mantle cell lymphoma. Curr Treat Options Oncol 2013;14(2):198-211

13. Mohamed A, Yu L, Backesjo C, et al. Bruton's tyrosine kinase (Btk) : function, regulation, and transformation with special emphasis on the PH domain. 2009;228(1): 58-73

14. Buggy JJ. Bruton tyrosine kinase (BTK) and its role in B-cell malignancy. Int Rev Immunol 2012;32(2):119-32

• Recommended references for further reading.

15. Satterthwaite AB, Witte ON. The role of Bruton's tyrosine kinase in B-cell development and function: a genetic perspective. 2000;175:120-7

16. Bruton O. Agammaglobulinemia. Pediatrics 1998;102(1 Pt 2):213-15

17. Ponader S. Burger J a. Bruton's Tyrosine Kinase: from X-Linked

Agammaglobulinemia Toward Targeted Therapy for B-Cell Malignancies. J Clin Oncol 2014;32(17):1830-9

18. Choi M, Kipps T. Inhibitors of B-cell receptor signaling for patients with B-cell malignancies. Cancer J 2013;18(5):404-10

19. Burger JA, Buggy JJ. Emerging drug profiles; Bruton's Tyrosine kinase (BTK) inhibitor ibrutinib (PCI-32765). Leuk Lymphoma 2013;54(11):2385-91

• Recommended references for further reading.

20. Baba Y, Hashimoto S, Matsushita M, et al. BLNK mediates Syk-dependent Btk activation. Proc Natl Acad Sci USA 2001; 98(5):2582-6

21. Psyrri A, Papageorgiou S, Liakata E, et al. Phosphatidylinositol 3'-kinase catalytic subunit alpha gene amplification contributes to the pathogenesis of mantle cell lymphoma. Clin Cancer Res 2009;15(18): 5724-32

22. 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

23. Niemann CU, Wiestner A. B-cell receptor signaling as a driver of lymphoma development and evolution. Semin Cancer Biol 2013;23(6):410-21

24. 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

•• Important and pivotal studies for ibrutinib in mantle cell lymphoma (MCL).

25. Cinar M, Hamedani F, Mo Z, et al. Bruton tyrosine kinase is commonly overexpressed in mantle cell lymphoma and its attenuation by Ibrutinib induces apoptosis. Leuk Res 2013;37(10):1271-7

26. Beà S, Valdés-Mas R, Navarro A, et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. Proc Natl Acad Sci USA 2013;110(45):18250-5

27. Pighi C, Gu T-L, Dalai I, et al. Phospho-proteomic analysis of mantle cell lymphoma cells suggests a pro-survival role of B-cell receptor signaling. Cell Oncol (Dordr) 2011;34(2):141-53

28. Hadzidimitriou A, Agathangelidis A, Darzentas N, et al. Is there a role for antigen selection in mantle cell lymphoma?

Immunogenetic support from a series of 807 cases. Blood 2011;118(11):3088-95

29. Rinaldi A, Kwee I, Taborelli M, et al. Genomic and expression profiling identifies the B-cell associated tyrosine kinase Syk as a possible therapeutic target in mantle cell lymphoma. Br J Haematol 2006;132(3): 303-16

30. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci USA 2010;107(29):13075-80

31. Bhatt V, Alejandro L, Michael A, Ganetsky A. The promising impact of ibrutinib, a Bruton's tyrosine kinase inhibitor, for the management of lymphoid malignancies. Pharmacotherapy 2013;34(3): 303-14

32. Maddocks K, Blum KA. Ibrutinib in B-cell Lymphomas. Curr Treat Options Oncol 2014;15(2):226-37

33. 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

•• Important and pivotal studies for ibrutinib in MCL.

34. Farooqui M, Lozier J, Valdez J, et al. Ibrutinib (PCI 32765) rapidly improves platelet counts in chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/SLL) patients and has minimal effects on platelet aggregation. Blood 2012;120: abstract 1789

35. Chang BY, Francesco M, De Rooij MFM, et al. Egress of CD19(+)CD5(+) cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. Blood 2013;122(14):2412-24

36. Cameron F, Sanford M. Ibrutinib: first global approval. Drugs 2014;74(2):263-71

37. Blum KA, Christian B, Flynn J, et al. A phase I trial of the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (PCI-32765), in combination with rituximab (R) and bendamustine in patients with relapsed/refractory non-Hodgkin's. Am Soc Hematol 2012;21(3):1643

38. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381(9873):1203-10

39. ClinicalTrials.gov. A study of the Bruton's tyrosine kinase inhibitor ibrutinib given in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. Available from: http://www.clinicaltrials.gov/show/NCT01776840

40. Flinn IW, Berdeja J, Freidbery J, et al. Combining ibrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP): updated results from a phase 1b study in treatment-naïve patients with CD20-positive B-Cell Non-Hodgkin's lymphoma (NHL). Blood 2013;122(21):852

41. ClinicalTrials.gov. A study combining ibrutinib. with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in patients with CD20-positive B-cell non Hodgkin lymphoma. Available from: http://clinicaltrials.gov/show/NCT01569750

42. Akinleye A, Chen Y, Mukhi N, et al. Ibrutinib and novel BTK inhibitors in clinical development. J Hematol Oncol 2013;6(1):59

43. Aalipour A, Advani RH. Bruton tyrosine kinase inhibitors: a promising novel targeted treatment for B cell lymphomas. Br J Haematol 2013;163(4):436-43

44. Middendorp S, Dingjan GM, Maas A, et al. Function of Bruton's tyrosine kinase during B cell development is partially independent of its catalytic activity. J Immunol 2003;171:5988-96

45. Yasuhiro T, Yoshizawa T, Daub H, et al. ONO-WG- 307, a novel, potent and selective inhibitor of Bruton's tyrosine kinase (Btk), results in sustained inhibition of the ERK, AKT and PKD signaling pathways. Cancer Res 2012;72:abstract 2021

46. Kozaki R, Yoshizawa T, Yasuhiro T, et al. Development of a Bruton's tyrosine kinase (Btk) inhibitor - ONO-WG-307, a potential treatment for B-cell malignancies. AACR 2012;857:abstract 857

47. Rule S, Shah N, Salles G, et al. A phase I study of the oral Btk inhibitor ONO-4059 in patients with relapsed/refractory B-cell lymphoma. Blood 2013; 122(21):abstract 4397

48. Salles G, Karlin L, Rule S, et al. A phase I study of the oral Btk inhibitor ONO-4059 in patients with relapsed/refractory and high risk chronic lymphocytic leukaemia (CLL). Blood 2013;122(21): abstract 676

49. Evans E, Tester R, Aslanian S, et al. Clinical development of AVL-292; a potent, selective covalent Btk inhibitor for the treatment of B cell malignancies. Blood 2011;118(21):3485

50. Brown J, Harb W, Hill H, et al. Phase Ib trial of AVL-292, a covalent inhibitor of Bruton's tyrosine kinase (Btk), in chronic lymphocytic leukemia (CLL) and B-non-Hodgkin lymphoma (B-NHL). Blood 2013;122(21):abstract 1630

51. ClinicalTrials.gov. A phase IB study Of The BTKi CC-292 combined with lenalidomide in adults patients with relapsed/refractory B-Cell lymphoma (CLEAR). Available from: http://clinicaltrials.gov/show/NCT01766583

52. Uckun F, Zheng Y, Cetkovic-Cvrlje M, et al. In vivo pharmacokinetic features, toxicity profile, and chemosensitizing activity of alpha-cyano-beta-hydroxy-betamethyl- N-(2,5-dibromophenyl) propenamide (LFM-A13), a novel antileukemic agent targeting Bruton's tyrosine kinase. Clin Cancer Res 2002;8(5):1224-33

53. Uckun F, Dibirdik I, Qazi S, et al. Anti-breast cancer activity of LFM-A13, a potent inhibitor of Polo-like kinase (PLK). Bio Org Med Chem 2007;15(2):800-14

54. Mahajan S, Ghosh S, Sudbeck E, et al. Rational design and synthesis of a novel anti-leukemic agent targeting Bruton's tyrosine kinase (BTK), LFM-A13 [alpha-cyano-beta-hydroxy-betamethyl- N-(2, 5-dibromophenyl)propenamide]. J Biol Chem 1999;274(14):9587-99

55. ClinicalTrial.gov. Safety, PK/PD, food effect study of orally administered HM71224 in healthy adult male volunteers. Available from: http://clinicaltrials.gov/show/NCT01765478

56. Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol 2009; 27(23):3822-9

•• Pivotal studies for licensed single agent drugs approved in relapsed/refractory MCL.

57. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol 2013;31(29):3688-95

•• Pivotal studies for licensed single agent drugs approved in relapsed/refractory MCL.

58. ClinicalTrials.gov. Study of ibrutinib (a Bruton's tyrosine kinase inhibitor), versus temsirolimus in patients with relapsed or refractory mantle cell lymphoma who have received at least one prior therapy. Available from: http://clinicaltrials.gov/show/NCT01646021

59. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet Oncol 2014;15(1):48-58

60. Hermine O, Hoster E, Walewski J, et al. Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT). Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final analysis of the MCL younger trial of the European mantle cell lymphoma network (MCL net) Blood 2012;120(21):abstract 151

61. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European. Blood 2005;105(7):2677-84

62. Pérez-Galán P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. Blood 2011; 117(1):26-38

63. Zucca E, Bertoni F. Toward new treatments for mantle-cell lymphoma? N Engl J Med 2013;369(6):571-2

64. ClinicalTrials.gov. Rituxan/bendamustine/PCI-32765 in relapsed DLBCL, MCL, or indolent non-Hodgkin's lymphoma. Available from: http://clinicaltrials.gov/show/NCT01479842

65. ClinicalTrials.gov. A long-term extension study of PCI-32765 (ibrutinib). Available from: http://clinicaltrials.gov/show/NCT01804686

66. ClinicalTrials.gov. Phase 2 ibrutinib + rituximab in relapsed/refractory mantle cell lymphoma (R/R MCL). Available from: http://clinicaltrials.gov/show/NCT01880567

67. ClinicalTrials.gov. Ublituximab + ibrutinib in select B-cell malignancies. Available from: http://clinicaltrials.gov/show/NCT02013128

68. ClinicalTrials.gov. Lenalidomide and ibrutinib in treating patients with relapsed or refractory B-cell non-Hodgkin lymphoma. Available from: http://clinicaltrials.gov/show/NCT01955499

69. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009;20(3):520-5

•• Pivotal studies for licensed single agent drugs approved in relapsed/refractory MCL.

70. Kouroukis C, Belch A, Crump M, et al. Flavopiridol in untreated or relapsed mantle-cell lymphoma: results of a phase II study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2003;21(9):1740-5

71. Renner C, Zinzani PL, Gressin R, et al. A multicenter phase II trial (SAKK 36/06) of single-agent everolimus (RAD001) in patients with relapsed or refractory mantle cell lymphoma. Haematologica 2012;97(7):1085-91

72. Witzig TE, Reeder CB, LaPlant BR, et al. A phase II trial of the oral mTOR inhibitor everolimus in relapsed aggressive lymphoma. Leukemia 2011;25(2):341-7

73. Eve HE, Carey S, Richardson SJ, et al. Single-agent lenalidomide in relapsed/refractory mantle cell lymphoma: results from a UK phase II study suggest activity and possible gender differences. Br J Haematol 2012;159(2):154-63

74. Ghielmini M, Schmitz SFH, Cogliatti S, et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). J Clin Oncol 2005;23(4):705-11