# Role of Tyrosine Kinase Inhibitors in Indolent and Other Mature B-Cell Neoplasms

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**ABSTRACT:** Targeting tyrosine kinases represents a highly specific treatment approach for different malignancies. This also includes non-Hodgkin lymphoma since it is well known that these enzymes are frequently involved in the lymphomagenesis. Hereby, tyrosine kinases might either be dysregulated intrinsically or be activated within signal transduction pathways leading to tumor survival and growth. Among others, Bruton's tyrosine kinase (Btk) is of particular interest as a potential therapeutic target. Btk is stimulated by B-cell receptor signaling and activates different transcription factors such as nuclear factor κB. The Btk inhibitor ibrutinib has been approved for the treatment of chronic lymphocytic leukemia and mantle-cell lymphoma recently. Numerous clinical trials evaluating this agent in different combinations (eg, with rituximab or classical chemotherapeutic agents) as a treatment option for aggressive and indolent lymphoma are under way. Here, we summarize the role of tyrosine kinase inhibitors in the treatment of indolent and other non-Hodgkin lymphomas (eg, mantle-cell lymphoma).

**KEYWORDS:** indolent lymphoma, treatment, tyrosine kinase inhibitors, Bruton's tyrosine kinase, pathogenesis

**SUPPLEMENT:** Tyrosine kinases in cancer

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## Introduction

Different receptor and nonreceptor tyrosine kinases play a crucial role in normal B-cell development and in the pathogenesis of indolent and aggressive B-cell neoplasms.[1–3] Therefore, targeting these structures is a promising treatment approach for these malignancies.[4] Comprehensive research elucidating the biological function of tyrosine kinases within different signal transduction pathways has been undertaken in recent years. Based on these findings, numerous clinical trials focusing on inhibitors of these enzymes have been conducted or are under way. Inhibition of the Bruton's tyrosine kinase (Btk) – a TEC family nonreceptor (cytoplasmic) tyrosine kinase involved in B-cell receptor (BCR) signaling – is of particular interest.[1,4] Hereby, BCR signaling might either be activated by chronic antigen stimulation or by an intrinsically increased BCR signaling activity (tonic BCR signaling).[1]

The novel Btk inhibitor ibrutinib has recently been approved for the treatment of chronic lymphocytic leukemia (CLL) and mantle-cell lymphoma (MCL). Likewise, receptor tyrosine kinases might be important in the pathogenesis of B-cell neoplasms and potentially be inhibited, such as the receptor tyrosine kinase-like orphan receptor 1 (ROR1), which is highly overexpressed in CLL and hairy cell leukemia (HCL).[5] Blocking this receptor in a CLL mouse model has shown therapeutic activity.[6] Targeting tyrosine kinases is not restricted to the malignant cell itself but might also affect the microenvironment. For example, osteoclast function was suppressed by the Btk inhibitor CC-292 in multiple myeloma (MM) and showed therapeutic potential when combined with the proteasome inhibitor carfilzomib.[7]

Here, we give an overview on the role of tyrosine kinase inhibitors in the treatment of different mature B-cell neoplasms, including CLL/small lymphocytic lymphoma (SLL), follicular lymphoma (FL), MCL, marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), HCL, and plasma cell dyscrasias (Table 1). Additionally, we summarize information on the biological function of tyrosine kinases within different signaling pathways, which might be involved in lymphomagenesis and might be targeted in the future.

## Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

The antigen-dependent BCR pathway plays an important role in the survival of CLL cells.[8] Blocking this pathway with the

**Table 1.** Clinical trials investigating tyrosine kinase inhibitors in CLL/SLL, FL, MCL, MZL, WM, HCL, and plasma cell dyscrasias.

| TYROSINE KINASE INHIBITOR [TARGETED TYROSINE KINASE*]/ TREATMENT REGIMEN | PHASE OF THE CLINICAL TRIAL | MALIGNANCY/ DISEASE STATUS (N) | OUTCOME | REFERENCE(S) |
|---|---|---|---|---|
| AZD2171 (cediranib) [VEGFR] | II | CLL/SLL, relapsed/ refractory (n = 15) | OR: none (trial closed early due to lack of efficacy) | 82 |
| Bafetinib [diverse kinases like Bcr-Abl, Lyn, Fyn] | II | CLL, relapsed/ refractory (n = 16) | OR: none [partial nodal response in 7/11 patients (64%)] | 83 |
| CC-292 [Btk] | I | CLL/SLL (n = 57), WM (n = 6), other B-NHL (n = 23), updated results for CLL/SLL (n = 83), relapsed/refractory | CLL/SLL: PR: 34%; all 17 efficacy-evaluable B-NHL patients reached SD, updated results for CLL/SLL: OR (PR): 31–67% (depending on dosage) | 84,85 |
| Dasatinib [diverse kinases like Bcr-Abl, Src and Btk] | II | MM, relapsed/`plateau phase´ (n = 21) | OR: 5% (subgroup of 6 patients after dose escalation: 17%) | 86 |
| | II | CLL/SLL, relapsed/refractory (n = 15) | OR (PR): 20% | 29 |
| Dasatinib [diverse kinases like Bcr-Abl, Src and Btk] + fludarabine | II | CLL, fludarabine-refractory (n = 20) | OR (PR): 17% | 30 |
| Dovitinib [FGFR] | II | MM, relapsed/refractory (n = 43) | OR: none, SD: 62% (patients with t(4;14)) vs 35% (patients without t(4;14)) | 72 |
| Entospletinib [Syk] | II | CLL, relapsed/refractory (n = 41) | OR (PR): 61% | 25 |
| | II | FL, relapsed/refractory (n = 41) | 55% with reduced tumor bulk (10% decreased in tumor bulk ≥50%), no CR | 33 |
| Fostamatinib [Syk] | I/II | phase II part: CLL/SLL (n = 11), FL (n = 21), MCL (n = 9), MZL (n = 3), DLBCL (n = 23), LPL (n = 1), relapsed/refractory | OR (phase II part): CLL/SLL: 55% (PR), FL: 10% (PR), MCL: 11% (PR), DLBCL: 22% (1 patient with CR), none of 3 evaluable patients with MZL or LPL responded | 24 |
| Ibrutinib (single agent) [Btk] | I | CLL/SLL (n = 16), FL (n = 16), MCL (n = 9), MZL (n = 4), WM (n = 4), DLBCL (n = 7), relapsed/refractory | OR (evaluable patients): 60% (CR 16%); ITT population: CLL/SLL: 69%, FL: 38%, MCL: 78%, MZL: 25%, WM: 75%, DLBCL: 29% | 34 |
| | I/II | CLL/SLL, treatment naïve (n = 31) | OR: 71% (CR: 13%) | 87 |
| | I/II | CLL/SLL, relapsed/ refractory (n = 85) | OR: 71% (CR: 2%), no difference between the patient groups (420 mg vs 840 mg ibrutinib daily), PFS 75% at 26 months | 13 |
| | II | CLL/SLL, presence of *TP53* aberration, different disease stages (n = 51) | OR: previously untreated: 97% (PR: 55%, PR with lymphocytosis: 42%), relapsed/refractory: 80% (PR: 40%, PR with lymphocytosis: 40%) | 10 |
| | II | MCL, relapsed/refractory (n = 111) | OR: 68% (CR: 21%), estimated median PFS: 13.9 months | 42 |
| | II | FL, relapsed/refractory (n = 40) | OR: 30% (CR: 3%) | 35 |
| | II | WM, relapsed/refractory (n = 63) | OR: 81%, major response rate (PR or better): 57% | 57 |
| | II | HCL, relapsed or `unfit´ (n = 8) | No detailed efficacy data available | 60 |
| | II** | MM, relapsed/refractory (n = 69) | OR (PR): 5%, up to 25% clinical benefit rate (depending on dosage) | 88 |

(*Continued*)

**Table 1.** (*Continued*)

| TYROSINE KINASE INHIBITOR [TARGETED TYROSINE KINASE*]/ TREATMENT REGIMEN | PHASE OF THE CLINICAL TRIAL | MALIGNANCY/ DISEASE STATUS (N) | OUTCOME | REFERENCE(S) |
|---|---|---|---|---|
| Ibrutinib [Btk] (vs ofatumumab) | III | CLL/SLL, relapsed/ refractory (n = 391) | OR (PR): 43% vs 4%, OS (at 12 months): 90% vs 81% | 16 |
| Ibrutinib [Btk] + bendamustine + rituximab | I | FL (n = 12), MCL (n = 17), MZL (n = 1), DLBCL (n = 16), transformed (n = 2), different disease stages | OR: 72% (FL: 90%, MCL: 94%, MZL: 100%, DLBCL: 37%, transformed: 50%); CR: 52% | 36 |
| | I | CLL/SLL, relapsed/refractory (n = 30) | OR: 93% (CR: 17%) | 89 |
| Ibrutinib [Btk] + lenalidomide | I | FL (n = 2), MCL (n = 2), LPL (n = 1), DLBCL (n = 4), transformed (n = 4), relapsed/ refractory | No detailed efficacy data available | 38 |
| | I | CLL/SLL, relapsed/refractory (n = 11) | OR (PR): 100% | 90 |
| Ibrutinib [Btk] + ofatumumab | I/II | CLL/SLL (n = 66), PLL (n = 2), transformed (n = 3), relapsed/ refractory | OR (CLL/SLL): 83% | 91 |
| Ibrutinib [Btk] + rituximab | II | CLL, high risk, different disease stages (n = 40) | OR: 95% (CR: 8%) | 92,93 |
| | II | MCL, relapsed/refractory (n = 50) | OR: 87% (CR: 38%) | 44 |
| Ibrutinib [Btk] + R-CHOP | I | FL (n = 4), MCL (n = 5), DLBCL (n = 24), treatment-naïve | OR: 91% (PR: 21%, CR: 70%) | 37 |
| Imatinib [Bcr-Abl, ckit] | II | MM, relapsed/refractory (n = 23) | OR: none, treatment ended in 18/23 patients (78%) due to PD | 75 |
| Imatinib [Bcr-Abl, ckit]*** + chlorambucil | I | CLL, relapsed/refractory (n = 11) | OR: 45% | 94 |
| Nintedanib (BIBF 1120) [VEGFR/FGFR/ PDGFR] | I | MM, relapsed/ refractory (n = 17) | OR: none, SD: 13% (evaluable patients) | 95 |
| ONO-4059 [Btk] | I | CLL, relapsed/refractory (n = 25) | OR (including modified PR with lymphocytosis): 84%, 89% responses in the 17p-deleted subgroup | 18,19 |
| | I | SLL (n = 1), FL (n = 3), MCL (n = 7), WM (n = 1), DLBCL (n = 2), relapsed/ refractory | OR (PR): 42%, OR for MCL: 50% | 96 |
| SB1518 [JAK2] | I | SLL (n = 1), FL (n = 10), MCL (n = 5), HL (n = 14), DLBCL (n = 4), relapsed/ refractory | OR at the highest dose level (n = 22): 14%, median PFS (all evaluable patients): 120 days | 40 |
| Sorafenib [different kinases such as VEGFR, PDGFR, ckit] | II | CLL (n = 2), FL (n = 4), MCL (n = 2), LPL (n = 1), DLBCL (n = 11), T-cell lymphoma (n = 1), relapsed/refractory | OR: 10%, SD: 42% | 97 |
| Sunitinib [different kinases such as VEGFR, PDGFR, ckit] | II | CLL/SLL, relapsed/refractory (n = 18) | OR: none (trial closed early due to lack of efficacy) | 82 |
| Vandetanib (ZD6474) [VEGFR/EGFR] | II | MM, relapsed/ refractory (n = 18) | OR: none | 80 |

**Notes:** Tyrosine kinase inhibitors are shown in an alphabetic order. *Some of the tyrosine kinase inhibitors inhibit further structures than those specified in this table. **Ibrutinib ± dexamethasone. ***Might also inhibit DNA repair.

**Abbreviations:** Btk, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FL, follicular lymphoma; HCL, hairy cell leukemia; HL, Hodgkin lymphoma; ITT, intention to treat; JAK2, Janus kinase 2; LPL, lymphoplasmocytic lymphoma; MCL, mantle-cell lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; OR, objective response; OS, overall survival; PD, progressive disease; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PLL, prolymphocytic leukemia; PR, partial response; R-CHOP, rituximab together with cyclophosphamide, doxorubicin, vincristine, and prednisolone; SD, stable disease; SLL, small lymphocytic lymphoma; VEGFR, vascular endothelial growth factor receptor; WM, Waldenstrom macroglobulinemia.

novel oral inhibitors appears to be highly active in relapsed/refractory CLL and even in high-risk disease defined by the presence of deletion 17p (del(17p)).[9,10]

One of the key kinases in the BCR pathway is Btk, which activates downstream survival signaling, including extracellular-signal regulated kinases 1/2 (ERK 1/2), phosphoinositide-3-kinases (PI3K), and the nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NF-κB) pathway.[11] Ibrutinib binds Btk covalently and thereby inhibits CLL cell proliferation, promotes apoptosis, and unleashes CLL cells from tissues into the blood.[12] In a phase Ib/II multicenter study, 85 patients with refractory/relapsed CLL/SLL were treated with different doses of ibrutinib orally attaining an overall response rate of 71%.[13] At month 26, an estimated progression-free survival (PFS) rate of 75% and overall survival (OS) of 83% were achieved (Table 1). These results were encouraging, especially in the high-risk setting as response was independent of clinical and genomic risk factors. Furthermore, toxicity was mild comprising transient diarrhea, fatigue, and upper respiratory tract infection.[13] Updated data from the 3-year follow-up of this trial showed that longer treatment with ibrutinib yielded an improved response quality. Treatment-related lymphocytosis was mostly asymptomatic even with a duration of >1 year and did not seem to impact PFS and OS. Toxicity including grade 3 or greater cytopenias, fatigue, and infections reduced during longer follow-up.[14] Furthermore, the comparison between ibrutinib and ofatumumab in a phase III trial recruiting pretreated patients with CLL/SLL showed a significantly longer PFS for ibrutinib-treated patients at 16 months (median not reached vs 8.1 months).[15,16] Additionally, OS was better in the ibrutinib arm with 85% vs 78% in the ofatumumab arm at 18 months, although 61% of patients randomized to the ofatumumab arm were censored because they had crossed over to ibrutinib. Patients treated with ibrutinib achieved a best overall response rate of 90% compared to only 25% in the ofatumumab subgroup.[15] Ibrutinib has been approved by the EMA and the FDA on the basis of the phase Ib/II study in 2014.[13] However, treatment fails in some patients. Performing whole exome sequencing in six relapsed patients, the acquired resistance to ibrutinib often involved mutation of a cysteine residue at the ibrutinib binding site (C481) and two additional mutations in phospholipase Cγ2 downstream of Btk.[17] Progression occurs mainly in patients with del(17p) and/or del(11q).[14]

Besides ibrutinib, several other Btk inhibitors are under clinical development. Preliminary data available on a phase I trial with ONO-4059 showed a favorable safety profile along with promising efficacy in 25 heavily pretreated CLL patients with a median treatment duration of 363 days. Best overall response rate was 84% with even 89% responses in the 17p-deleted subgroup.[18,19] Furthermore, ACP-196, a next-generation Btk inhibitor, is currently under investigation as a single agent or within combination therapy in phase I/II clinical trials.

Spleen tyrosine kinase (Syk) is a cytoplasmic tyrosine kinase and a mediator of BCR signaling. Activation of Syk is important for cell survival and proliferation in CLL.[20,21] Syk also influences retention of CLL cells within lymphoid tissues and chemotaxis.[22,23] Disrupting the BCR pathway by Syk inhibitors is another therapeutic approach for CLL. However, it seems to be less efficient than Btk inhibition. Fostamatinib attained partial remission in 55% of eleven patients with CLL/SLL.[24] Entospletinib, another selective Syk inhibitor, was assessed in a phase II study that enrolled 41 CLL patients among patients with other non-Hodgkin lymphoma. At 24 weeks, the PFS rate was 70% with a median PFS of 13.8 months and an objective response rate of 61%. Entospletinib was generally well tolerated, and the most common side effects included dyspnea, pneumonia, febrile neutropenia, dehydration, and pyrexia.[25]

Dasatinib, a tyrosine kinase inhibitor originally developed for the treatment of chronic myelogenous leukemia, inhibits several kinases (eg, Bcr-Abl, Src, Btk), whereas some of them are activated within CLL cells too.[26–28] When used in clinical trials, dasatinib achieved only a low partial remission rate of 20% in a phase II study encompassing 15 patients with CLL/SLL.[29] In combination with fludarabine, even inferior response was achieved in fludarabine-refractory patients (17% of patients with partial remission).[30]

## Follicular Lymphoma

Dysregulation of expression and/or activation in cytoplasmic and receptor tyrosine kinases is observed in FL cells too. Although the impact of tonic BCR signaling in the pathogenesis of FL is still not well understood yet, the BCR-mediated activation of the tyrosine kinase Syk appears to be altered in FL.[31] Newer *in vitro* data showed that Syk is not only overexpressed in FL cells but also involved in the high expression of matrix metalloproteinase 9 and vascular endothelial growth factor (VEGF), thereby putatively promoting invasion and angiogenesis.[32] In spite of these promising data, using Syk inhibitors like fostamatinib in clinical trials for relapsed/refractory FL resulted in an objective response rate of only about 10% of treated patients.[24] In a more recent phase II trial, another selective Syk inhibitor (entospletinib) was evaluated in the same patient population and also a substantial tumor bulk reduction (≥50%) was reported in only 10% of treated patients.[33]

More mature data regarding inhibition of tyrosine kinases involved in BCR signaling of FL were obtained by using ibrutinib in relapsed and de novo FL. Two phase I/II trials with monotherapy in relapsed FL resulted in very similar results with an objective response rate of 38% (6/16 patients, three patients with complete remission) and 30% (including one patient with complete remission) in 40 treated patients, respectively.[34,35] Although active, ibrutinib monotherapy appears to be less effective in FL patients when compared to CLL or MCL, an observation that might reflect differences

in chronic BCR signaling between the separate non-Hodgkin lymphoma entities. Nevertheless, combining this approach with rituximab and bendamustine improves the objective response rate in relapsed/refractory FL to up to 90%.[36] Further phase I trials combining ibrutinib with lenalidomide in relapsed FL or with rituximab together with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) in treatment-naïve FL reported encouraging safety and efficacy results.[37,38]

Since VEGF has been shown to be overexpressed in FL cells, interfering with receptor tyrosine kinase VEGF signaling in the malignant cells or the microenvironment appears to be a logical consequence. In this regard, testing the angiogenesis inhibitor bevacizumab in addition to rituximab in a randomized phase II trial resulted in a significant increase in PFS.[39] As another target for selective inhibition of tyrosine kinases, interfering with cytokine-mediated janus kinase 2 activation led to some objective responses in tumor size in FL patients.[40]

In summary, inhibition of BCR-activated tyrosine kinases shows clinical efficacy in FL patients. Further investigations, especially in combination therapy approaches, will provide additional data on the impact of this therapeutic principle in the treatment of FL patients. In addition, inhibition of tyrosine kinases involved in growth factor or cytokine signaling might be another promising way for further investigations.

## Mantle-Cell Lymphoma

Still being considered an incurable disease, there is no standard upfront treatment regimen for MCL. Typically, three regimens are used, each in combination with rituximab: R-CHOP, bendamustine (R-B), and cyclophosphamide, vincristine, and prednisolone (R-CVP). Despite a usually good initial response, MCL tends to recur early and shows an aggressive course in most patients.[41] Hence, there is a need for treatment options with tolerable side effects.

Being an attractive target for selective B-cell inhibition, ibrutinib has been studied as a single substance in MCL. In a phase I study, nine patients with MCL were treated with ibrutinib. Seven patients showed a response, of which three had a complete response.[34] On the basis of these results, a phase II study was conducted with 111 patients with MCL who received ibrutinib at a dose of 560 mg daily until disease progression or the occurrence of unacceptable side effects.[42] They had received a median of three therapies before and were stratified according to prior treatment without ($n$ = 63) or with bortezomib ($n$ = 48). A total of 68% of the patients ($n$ = 75) responded, with 21% having a complete and 47% a partial response; there was no significant difference between bortezomib-pretreated and bortezomib-naïve patients. With regard to the secondary endpoints, the estimated median response duration was 17.5 months, the estimated median PFS was 13.9 months, and the median OS was not reached. Moreover, the estimated rate of OS at 18 months was 58%. Treatment was generally well tolerated; most common adverse events comprised mild-to-moderate fatigue, nausea, diarrhea, and grades 3 and 4 hematologic adverse events, including neutropenia in 16%, thrombocytopenia in 11%, and anemia in 10% of the MCL patients. Ibrutinib showed activity in all analyzed subgroups regardless of the presence or absence of blastoid disease, bulky disease, advanced disease, refractory disease, previous high-intensity therapy, or previous therapy with lenalidomide.[42] Given the fact that most patients had a long-standing, heavily pretreated disease, this study formed the base for the US FDA's Breakthrough Therapy Designation Pathway.[43] The encouraging results spurred the initiation of several trials investigating the combination of ibrutinib with rituximab alone, rituximab and bendamustine, ublituximab or lenalidomide, and comparing ibrutinib against temsirolimus, thus further enhancing the therapeutic possibilities in this disease.[36–38,44] In fact, ibrutinib showed the highest response rate when compared to cladribine, lenalidomide, temsirolimus, rituximab, 90Y-ibritumomab tiuxetan, and everolimus.[45] Several other tyrosine kinase inhibitors are currently studied in MCL besides the Btk inhibitor ibrutinib, such as the Syk inhibitor fostamatinib.

## Marginal Zone Lymphoma

Compared to other indolent B-cell lymphoma (eg, CLL), limited data has been published on the role of tyrosine kinases in the pathogenesis of MZL. Moreover, larger clinical studies investigating kinase inhibitors are lacking for patients with MZL. One possible reason is the fact that the incidence of MZL is lower than that of other indolent B-cell lymphomas.[46] However, it has also to be mentioned that MZL might be cured by anti-infective strategies alone, such as *Helicobacter pylori* eradication for early-stage gastric mucosa-associated lymphoid tissue (MALT) lymphoma.[47] Despite this, targeting tyrosine kinases – in particular in the BCR pathway – might be an important therapeutical approach for MZL.[1] For example, BCR binding of the E2 envelope protein of hepatitis C virus – potentially associated with chronic BCR activation – has been described in extranodal MZL, a fact which might explain their causal relationship.[1,48,49]

Patients with MZL have been included in previous and ongoing clinical trials evaluating inhibition of BCR signaling by ibrutinib.[34] A phase I trial evaluating ibrutinib in relapsed or refractory B-cell lymphoma encompassed three evaluable patients with MZL and reported partial response, stable disease, and progressive disease in each one of them.[34] Besides Btk, the nonreceptor tyrosine kinase Syk is controlled by BCR signaling. A phase I/II trial evaluating fostamatinib was conducted based on the data that Syk inhibition induced apoptosis in various B-cell lines and inhibited lymphoma growth in a xenograft model.[24,50] Three patients with MZL were included, but none of them showed an objective response.[24]

A further tyrosine kinase that might be involved in the pathogenesis of MZL is the orphan receptor tyrosine kinase

ROR1. It is highly overexpressed in CLL and HCL, but can also be detected in a subset of MZL patients.[5,51] Growing evidence suggests that this tyrosine kinase is a survival factor, and thus might be a potential therapeutic target in different malignancies, including MZL.[5,6] Antiangiogenesis treatment using VEGF receptor antibodies might be another interesting approach for gastric MALT lymphoma. It was already demonstrated in a mouse model that these antibodies decreased significantly the size of the tumor accompanied by apoptotic changes of the endothelial cells belonging to the microvascular network.[52,53]

## Waldenstrom Macroglobulinemia

Potential molecular targets for tyrosine kinase inhibitors in WM have only recently been detected. Unlike other B-cell neoplasms such as CLL or diffuse large B-cell lymphoma, the role of the BCR signalosome in the biology of WM remains poorly understood.[49,54] The myeloid differentiation factor 88 (MYD88) L265P somatic mutation occurs in more than 90% of patients with WM or lymphoplasmocytic lymphoma (LPL). Thus, detection of this mutation might help to differentiate WM or non-IgM LPL from other similar B-cell disorders.[55,56]

MYD88 and its two adapter proteins Btk and Toll/interleukin-1 receptor (TIR) domain containing adaptor protein (TIRAP) are activated after Toll-like receptor 4 binds to its ligand. MYD88 might also directly be activated by ligand binding of interleukin-1 receptor.[55] Further downstream signaling promotes the activation of NF-κB-dependent prosurvival pathways. WM cells with the L265P mutation in the MYD88 gene have enhanced proliferation and survival.[56] Although the exact signaling cascade remains unclear, it has been shown that the abrogation of Btk binding to MYD88 results in inhibition of NF-κB signaling and apoptosis.[56] Therefore, Btk appears to be a potential therapeutic target for tyrosine kinase inhibitors in WM as well. In fact, a recently conducted phase II trial investigating the Btk inhibitor ibrutinib in previously treated patients with WM ($n = 63$) demonstrated a best overall response rate of 81% with a major response rate (partial response or better) of 57% leading to approval by the FDA.[57] Further phase II and III trials investigating different Btk inhibitors in WM are under way.

Taken together, tyrosine kinase inhibitors seem to complement the already existing armory of alkylating agents, nucleoside analogs, monoclonal antibodies, and proteasome inhibitors to treat WM and might be even used in combination therapies.

## Hairy Cell Leukemia

Alterations in the BCR-mediated signaling pathways are also crucial for the pathogenesis of HCL.[1,58] With respect to their BCR, canonical (ie, nonrandom, potentially antigen-driven) somatic hypermutation was observed in rearrangements of classical HCL and to a lesser extent also in HCL variant.[59] In addition, Btk has recently been identified as a promising target in patients with HCL and clinical trials investigating the Btk inhibitor ibrutinib in these patients are ongoing.[60,61]

As aforementioned, ROR1 is highly overexpressed in HCL compared to healthy controls and other indolent lymphomas such as FL.[5] ROR1 is part of the Wnt pathway with Wnt5a presumably being its ligand.[5,62] It is important for organogenesis but its role in HCL remains largely unknown.[63] Additionally, increased expression of Src – a proto-oncogene with tyrosine-specific protein kinase activity – has been reported in HCL and might be an interesting therapeutic target.[64]

In conclusion, tyrosine kinase inhibitors offer a promising new therapeutic tool for HCL besides BRAF inhibitors such as vemurafenib and dabrafenib after decades of interferon, chemotherapy, and lately monoclonal antibodies, but randomized controlled data are not available yet. Given the low incidence and the prolonged natural course of HCL, it will most likely take decades again to gain evidence on that topic.

## Plasma Cell Dyscrasias

Various tyrosine kinases are dysregulated in clonal vs normal plasma cells and might play an important role in the pathogenesis of plasma cell dyscrasias. The translocation t(4;14) – usually a primary event – is detected in 10%–20% of all patients with MM and associated with an unfavorable outcome.[65–67] Presence of t(4;14) frequently results in dysregulated expression of fibroblast growth factor receptor 3 (FGFR3), a receptor tyrosine kinase.[68] However, FGFR3 might also be activated constitutively after somatic mutation at a later disease stage. It acts through the mitogen-activated protein kinase pathway and promotes tumor progression in MM.[68,69] Dovitinib (CHIR-258) is a receptor tyrosine kinase inhibitor, which showed inhibitory activity against various receptors, including FGFR *in vitro* and induced tumor growth reduction in a MM xenograft model with activating FGFR3 mutations.[70,71] Based on these promising preclinical data, a phase II study evaluating this agent in patients with relapsed or refractory MM was recently conducted.[72] Objective response was not observed in any patient, although 62% of patients carrying t(4;14) (vs 35% of patients lacking this translocation) showed disease stabilization. Despite this, dovitinib might have a role as part of a combination regimen in MM treatment.

CD117 (ckit), a receptor tyrosine kinase activated by its ligand stem cell factor is expressed by clonal plasma cells in about 30% of MM patients, 45% of patients with smoldering MM (SMM), and 70% of patients with monoclonal gammopathy of undetermined significance (MGUS).[73] Conversely, normal plasma cells are uniquely $CD117^-$.[74] Despite the fact that the biological function of ckit is largely unknown in plasma cell dyscrasias, it was shown that its expression is associated with an altered maturation of the myeloid and lymphoid hematopoietic cells in the bone marrow.[73] Imatinib, which inhibits ckit besides Bcr-Abl, has been evaluated as a

treatment option for refractory/relapsed MM but did not have significant efficacy.[75]

Furthermore, the proline-rich tyrosine kinase 2 (Pyk2), a nonreceptor protein kinase belonging to the focal adhesion kinase family, is overexpressed in MM, SMM, and MGUS compared to normal bone marrow.[76] Interestingly, it has also been demonstrated that Pyk2 might be an effector of FGFR3 activation, which regulates cell survival as aforementioned.[77] Pyk2 silencing suppressed Wnt/ß-catenin signaling and reduced MM cell proliferation, adhesion, and cell cycle progression.[76] In addition, Pyk2 silencing prolonged survival in an MM xenograft model.[76] Taken together, these data indicate that Pyk2 might be involved in the pathogenesis of plasma cell dyscrasias and be a potential therapeutic target in the future.

Although clonal plasma cells, like other B-cell neoplasms, express the cytoplasmic nonreceptor tyrosine kinase Btk, its inhibition by the novel Btk inhibitor CC-292 had no potent anti-MM activity *in vitro*.[7,78] This observation might be explained by the specific *in vitro* conditions (including a low CC-292 dose) used in this study.[7] However, Btk is also expressed by osteoclasts that contribute to bone destruction in MM.[78] It was shown that CC-292 suppresses osteoclast function, in particular if combined with the proteasome inhibitor carfilzomib.[7] A multicenter phase I/II trial evaluating the combination of carfilzomib together with ibrutinib in patients with refractory or relapsed MM is currently ongoing.

In summary, tyrosine kinase inhibitors do not play a role in the clinical routine treatment of plasma cell dyscrasias yet. However, several tyrosine kinase inibitors (eg, ibrutinib, PTK787/ZK222584) are further explored in vitro and in vivo in MM and might play a role in the treatment of this disease in the future.[79–81]

## Conclusion

Recently published phase I and II trials demonstrated promising objective response rates of 70%–90% by using ibrutinib as a single agent for relapsed or refractory CLL and MCL. Ibrutinib is characterized by a favorable toxicity profile, and preliminary data suggest that ibrutinib-induced lymphocytosis has no adverse impact on outcome. It is noteworthy that ibrutinib showed high rates of remission even in CLL patients having adverse cytogenetic changes like del(17p). First data demonstrate that ibrutinib, given as a single agent, has a similar efficacy in WM than it has in CLL or MCL. In contrast, the substance, used as monotherapy, has only moderate activity in FL exhibiting an objective response rate of about 30%. Combined with classical chemotherapy or monoclonal antibodies, ibrutinib is currently under investigation in different subtypes of indolent lymphomas. Other tyrosine kinase inhibitors are evaluated as well, of which the Syk inhibitors, fostamatinib and entospletinib, might be of particular interest in the near future. But also elucidating resistance mechanisms is important as possible combination therapies might help to overcome these in the future. Research does not stop here, however, and next-generation Btk inhibitors are already in sight.

## Author Contributions

Contributed to the writing of the manuscript: NK, RM, RR, TKH, MSH. Agree with manuscript results and conclusions: NK, RM, RR, TKH, MSH. Jointly developed the structure and arguments for the paper: NK, RM, RR, TKH, MSH. Made critical revisions and approved final version: NK, RM, RR, TKH, MSH. All authors reviewed and approved of the final manuscript.

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