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Protein kinase inhibitors against malignant lymphoma

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Abstract

Introduction—Tyrosine kinases (TKs) are intimately involved in multiple signal transduction pathways regulating survival, activation, proliferation and differentiation of lymphoid cells. Deregulation or overexpression of specific oncogenic TKs is implicated in maintaining the malignant phenotype in B-lineage lymphoid malignancies. Several novel targeted TK inhibitors (TKIs) have recently emerged as active in the treatment of relapsed or refractory B-cell lymphomas that inhibit critical signaling pathways, promote apoptotic mechanisms or modulate the tumor microenvironment.

Areas covered—In this review, the authors summarize the clinical outcomes of newer TKIs in various B-cell lymphomas from published and ongoing clinical studies and abstracts from major cancer and hematology conferences.

Expert opinion—Multiple clinical trials have demonstrated that robust antitumor activity can be obtained with TKIs directed toward specific oncogenic TKs that are genetically deregulated in various subtypes of B-cell lymphomas. Clinical success of targeting TKIs is dependent upon on identifying reliable molecular and clinical markers associated with select cohorts of patients. Further understanding of the signaling pathways should stimulate the identification of novel molecular targets and expand the development of new therapeutic options and individualized therapies.

Keywords

BTK; kinase inhibitor; lymphoma; protein kinase; SYK

1. Introduction

Malignant lymphoma is the fifth most common cancer in the US and its incidence has been increasing in the past three decades. Non-Hodgkin's lymphoma (NHL) represents the most prevalent form of malignant lymphoma. The most common NHL subtypes are diffuse large

B-cell lymphoma and follicular lymphoma. Mantle cell lymphoma is one of the most difficult-to-treat subtypes of NHL. In recent years, advances in NHL have produced information critical to our understanding of cell growth, proliferation and cell death. The intracellular machinery and signaling cascades that are active in lymphomas have been dissected and revealed multiple potential molecular targets for new agents that inhibit critical signaling pathways, promote apoptotic mechanisms or modulate the tumor microenvironment. Inhibiting these pathways may result in significant clinical benefit for patients. These advances in our understanding of the biology of NHL, especially B-lineage NHL, have spawned several clinical investigations of inhibitors of regulatory kinases, and some appear to have clinically relevant single-agent activity in B-lineage NHL. Multiple clinical trials have demonstrated that robust antitumor activity can be obtained with kinase inhibitors directed toward specific oncogenic tyrosine kinases (TKs) that are genetically dysregulated [1,2]. In this review, we summarize the clinical activity profiles of various kinase inhibitors that are in clinical development as new drug candidates against NHL.

1.1 Targeting B-cell receptor signaling pathways in B-cell lymphomas

The B-cell receptor (BCR) plays an important role in normal B-cell development. Bone marrow progenitor B cells that express a functional BCR differentiate into mature B cells in secondary lymphoid organs, whereas those B-cell precursors that fail to express a BCR undergo apoptosis [3]. BCR cross-linking leads to activation of protein tyrosine kinases (PTKs): the SRC family PTKs Lyn, Fyn, Blk and Lck, which in turn results in the recruitment of the spleen tyrosine kinase (SYK), and the TEC family kinase Bruton's tyrosine kinase (BTK) (Figure 1). The recognition of antigen by the BCR results in B-cell proliferation and differentiation into antibody-secreting plasma cells [4]. BCR signaling has been shown to be important for the growth of B-cell NHL, and several studies have shown that BCR signaling is also directly involved in the development of some B-cell NHLs [5]. Furthermore, Epstein-Barr virus is able to promote the development of BCR-negative B-cell NHL by activation of proteins involved in the signaling pathway downstream of BCR, such as phosphatidylinositol 3-kinase (PI3K) and acutely transforming retrovirus (AKT), emphasizing the role of the BCR signaling proteins in B-cell lymphomagenesis [6]. SYK activation functions to amplify the BCR signal and connects the BCR with important major pathways such as PI3K/AKT [7]. Recent investigations have focused on developing inhibitors to the SYK and BTK components of the signaling pathway.

1.1.1 SYK Inhibitors—The tyrosine kinase SYK is critical for normal B-cell development and proliferation and recent studies implicate this protein in the NHL pathogenesis. In particular, SYK is a key component of the BCR signaling pathway [8]. Given the vital role of SYK in BCR signaling, pharmacological or genetic targeting of SYK has been pursued as a therapeutic strategy for the treatment of NHL. SYK inhibition by using a chemical SYK inhibitor or by small interfering RNA (siRNA) results in potent inhibition of mammalian target of rapamycin (mTOR) activity in mantle cell lymphoma (MCL), large cell lymphoma and Burkitt's lymphoma [9]. Targeting BCR signaling pathways appears to be a highly promising therapeutic strategy in B-cell lymphomas.

The majority of SYK inhibitors undergoing clinical development target the conserved ATP-binding site within the catalytic domain of the kinase [10–13]. Because of the similarities of the ATP pocket structures among different kinases, the ATP-competitive SYK inhibitors affect multiple TKs such as RET, KIT, JAK 1-3, FLT3, PDGFR- α , Aurora, LCK, KDR as well as adenosine A3 receptor and have off-target effects that lead to undesirable side effects such as hypertension, myelosuppression, teratogenicity, neutropenia or auto-immune diseases. Moreover, as SYK is widely distributed in different cell types, inhibiting its catalytic activity bears the risk of unwanted consequences on various physiological

functions such as cell differentiation, adhesion and proliferation [11]. The lead SYK inhibitors in clinical trials include R406, R788, CG14979 and PRTO62607. Several of these ATP-binding site SYK inhibitors are under clinical trials in patients with B-cell lymphomas [10]. In addition, more specific small molecule substrate-binding (P) site SYK inhibitors as well as antisense oligonucleotides and siRNAs have also been developed to selectively knock down SYK [12]. The availability of both ATP-binding site inhibitors (e.g., R-406) and P-site inhibitors (e.g., C-61) of SYK may be particularly helpful in patients with SYK mutations that might influence inhibitor binding to ATP- and/or substrate-binding sites. Recent studies have established SYK kinase as a potential therapeutic target in NHL, CLL and acute myeloid leukemia.

Fostamatinib disodium (FosD/R788, (6-({5-fluoro-2-((3,4,5-trimethoxyphenyl)amino)pyrimidin-4-yl}amino)-2,2-dimethyl-3-oxo-2H-pyrido[3,2-b][1,4]oxazin-4(3H)-yl)methyl dihydrogen phosphate, disodium; AstraZeneca) is the first SYK inhibitor available that has been moved to the clinic. R788, a pro-drug of R406 is an oral ATP-competitive SYK inhibitor with demonstrated antitumor activity both *in vitro* and *in vivo*. In a Phase I/II clinical trial, Friedberg *et al.* [13] investigated R788 in patients with relapsed and refractory (R/R) B-cell NHL and CLL. In the Phase I part of the trial, two cohorts of six patients each received one of two dose levels, 200 or 250 mg, BID orally. All patients in cohort 1 had stable disease after treatment with R788 with a median duration of 5.3 months. In cohort 2, one patient with FL displayed a partial response (PR) with a response duration of 13.3 months. The dose-limiting toxicities were neutropenia, diarrhea and thrombocytopenia. In the Phase II study, 68 patients with recurrent B-NHL were treated with R788 (200 mg BID). The highest response rate (55%) was observed in patients with SLL/CLL. Objective response rates were also noted in DLBCL (22%), FL (10%) and MCL (11%) (Table 1). The median PFS was 4.2 months for all patients. Thus, differences in response rates among different NHL subtypes may be owing to biologic heterogeneity. Common toxicities observed in this study included diarrhea, fatigue and cytopenias. The authors speculated that inhibition of SYK may have disrupted the nodal microenvironment and led to increased trafficking of CLL cells out of nodal tissues and into the peripheral blood where they would then eventually die.

Because of the similarities of the ATP pocket structures among different kinases, the ATP-binding site SYK inhibitors affect multiple tyrosine kinases and have off-target activities. Indeed, hypertension, a common and potentially dangerous side effect of FosD, has been attributed to off-target inhibition of vascular endothelial growth factor receptor (VEGFR). Inhibitors targeting the substrate-binding sites of TKs are hoped to have enhanced specificity and potency [14]. Unlike available inhibitors of SYK targeting the ATP-binding site, C-61 targets the tyrosine kinase substrate-binding site of SYK [15] and thereby provides a unique opportunity to selectively target the SYK-dependent antiapoptotic blast cell survival machinery that is controlled by the TK activity of SYK, especially *via* tyrosine phosphorylation events leading to activation of signal transducer and activator of transcription 3 (STAT3) and PI3-kinase [16].

1.1.2 BTK Inhibitors—Like SYK, BTK is also intimately involved in multiple signal transduction pathways regulating survival, activation, proliferation and differentiation of B-lineage lymphoid cells [17]. A meta-analysis of cancer-associated gene expression changes utilizing the Oncomine database revealed a marked enrichment of the most discriminating BTK-dependent anti-apoptotic gene targets in 17 comparisons for diagnostic classes of human lymphomas and leukemias obtained from eight studies [18]. Consequently, BTK has emerged as a new molecular target for treatment of B-lineage NHL and leukemias.

Both covalent and noncovalent BTK inhibitors are being developed as therapeutic agents for various indications [18-20]. The clinically most advanced irreversible BTK inhibitor Ibrutinib/PCI-32765 ((*R*)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one; Pharmacyclics) has demonstrated clinical activity against a variety of B-cell malignancies in ongoing Phase I/II trials including MCL, CLL, FL and DLBCL, with good tolerability. Likewise, dianilinopyrimidine-based irreversible BTK inhibitor AVL-292 (Avila Therapeutics/Celgene), a multikinase inhibitor, has promising *in vitro* activity against lymphoma cells. Dasatinib, a BCR-ABL kinase inhibitor that is US FDA approved for treatment of chronic myelogenous leukemia (CML), is a potent inhibitor of BTK [21]. Ibrutinib/PCI-32765 is being investigated in patients with B-lineage lymphoid malignancies, including patients with relapsed/refractory CLL/small lymphocytic lymphoma (SLL), MCL, DLBCL, FL and multiple myeloma (MM). In Phase I/II studies, PCI-32765 showed encouraging clinical activity in patients with several types of B-cell lymphoma [22].

1.1.2.1 Multiple R/R B-cell malignancies: Advani *et al.* [23] reported a dose-escalating Phase I study of PCI-32765 (1.25 mg/kg/day to 12.5 mg/kg in a 28-day cycle) in 56 patients with multiple histologic subtypes of B-cell NHL. The overall response rate (ORR) was achieved in 30 (62%) of 50 evaluable patients including 7 complete responses (CRs) and 23 partial responses (PRs). Responses were achieved in 11 (79%) patients with CLL/SLL, 7 (78%) with MCL, 6 (46%) with FL, 3 (75%) with Waldenström's macroglobulinemia (WM), 2 (29%) with DLBCL and 1 (33%) with MZL. Median progression-free survival (mPFS) in all patients was 13.6 months. Therapy was well tolerated and grade 3 or higher adverse effects (AEs) observed were neutropenia, thrombocytopenia and anemia (< 20%). A second Phase I study by Fowler *et al.* [24] in 47 patients with various R/R B-cell malignancies, a dose of 420 mg daily was established based on > 90% occupancy of BTK. In this study, PCI-32765 induced a durable objective response (OR).

1.1.2.2 R/R MCL: Interim analysis of a Phase II study in patients with R/R MCL, Staudt *et al.* [25] showed that PCI-32765 (560 mg daily in 28-day cycles) produced an ORR of 67%; in patients pretreated with Bortezomib (Velcade), the ORR was 75%, compared with 58% in Bortezomib-naïve patients. Hematologic grade 3/4 AEs occurred in < 5% of patients. Wang *et al.* [26] reported the results of a Phase II study of PCI-32765 in R/R MCL patients. In the study, 111 patients (Bortezomib-naïve and Bortezomib-exposed), received oral PCI-32765 (560 mg daily). The primary endpoint of the study is ORR. Duration of response and safety evaluation was secondary endpoints. The median follow-up time was 9.2 months, with a range of time to response to treatment of 1.4–16.4 months. The study showed an ORR of 68% (22% CR and 46% PR) with a median PFS estimated at 13.9 months. Results were similar between the Bortezomib-naïve and Bortezomib-exposed patients. Long-term follow-up of the initial 51 patients showed an incremental improvement in the response rate over time. The ORR increased for this patient subset to 75%. PCI-32765 resulted in high and durable responses and was generally well tolerated. Pneumonia was the only grade 3 or higher treatment-emergent AE occurring in 5% of patients. A randomized, multicenter Phase III trial comparing PCI-32765 with Temsirolimus as a monotherapy has been initiated in R/R MCL patients who received at least one prior Rituximab-containing chemotherapy regimen. The primary endpoint of the study is PFS when compared with Temsirolimus. This study is planned to enroll 280 patients outside the US. Recently, the US FDA has granted 'Breakthrough Therapy' designation to Ibrutinib monotherapy for the treatment of patients with R/R MCL.

1.1.2.3 R/R DLBCL: Wilson *et al.* [27] reported the results of a Phase II study of PCI-32765 in 70 patients with R/R DLBCL in two genetically distinct subtypes of DLBCL,

the activated B-cell (ABC) subtype and the germinal center (GC) subtype. The ABC subtype appears to be more driven by BCR signaling. The ORR in the heavily pretreated population was 23%. Responses were primarily in the ABC subtype with 12 of 29 patients (41%) responding (5 CR and 7 PR). Grade 3 or higher AEs were 5–10% of the patients.

1.1.2.4 R/R CLL or SLL: Daily oral administration of PCI-32765 has been evaluated in patients with R/R CLL or SLL that had been treated with at least two prior therapies, including Fludarabine [28]. In an ongoing Phase Ib/II study in patients with R/R CLL or SLL, 61 patients with R/R CLL were enrolled at two dose levels, 420 mg (n = 27) or 840 mg (n = 34). Serious grade 3 or 4 infections were noted in 25% of patients in the 420 mg cohort and 29% patients in the 840 mg cohort. Treatment was associated with an early increase in lymphocytosis that began around 1 week and persisted for several months in the majority of patients. With a median follow-up of 12.6 months in the 420 mg cohort and 9.3 months in the 840 mg cohort, the ORR for the 420 mg dose level was 67% and for the 840 mg dose 68%. In addition, 6 (22%) and 8 (24%) of patients in the 420 and 840 mg cohort had a nodal response with persistent lymphocytosis. The 1-year estimated PFS for the patients enrolled on this study is 86% [28]. These data indicate that PCI-32765 is highly active and well tolerated in CLL/SLL patients, irrespective of high-risk genomic abnormalities and suggests that this drug may be an important new targeted treatment approach for CLL, particularly in combination with other agents.

Recently, O'Brien *et al.* [29] reported the updated results of a Phase Ib/II trial in R/R CLL (n = 61) and treatment-naïve (TN) CLL (n = 31) patients enrolled at two fixed continuous dose levels of PCI-32765 single agent (420 and 840 mg). In addition to the data reported by Byrd *et al.* [30,31], on the TN patients, this report provided updated PFS data in the R/R patient population. With a median follow-up of 17.5 months, PFS in the 420 mg cohort was 87.7%. High-risk R/R patients with 17p deletion (n = 20) and IgVH unmutated status (n = 42) have an estimated 18-month PFS of > 70 and > 80%, respectively. In the TN 420 mg dose cohort patients (65 years old), the ORR was 81%, which included a 12% CR rate. Fifty percent of patients with pretreatment cytopenias have experienced sustained improvement in hemoglobin and/or platelet levels. The estimated PFS in the TN patients at 15 months is 96% in the 420 mg cohort. Recently, Byrd *et al.* [30,31] reported the results of a Phase Ib/II study of Ibrutinib in subjects with CLL/SLL either R/R (n = 85) or TN (n = 31) patients (65 years) designed to assess safety, tolerability and efficacy at two dose levels (420 or 840 mg daily). Among 116 patients, the ORR was 68% in TN patients with an estimated 96% PFS rate at 26 months. In patients with RR CLL/SLL, the ORR was 71% with an estimated PFS at 26 months of 75%. Responses were independent of high-risk clinical or genetic features, such as a deletion of part of chromosome 17 (del17p). Grade 3–4 toxicities (10–13%) included diarrhea, infection and hematologic toxicity (anemia and thrombocytopenia). There was no evidence of cumulative toxicity or long-term safety concerns. With a maximum follow-up of 26 months, it was estimated that 96% of the TN and 75% of the R/R high-risk patients are without progression.

Currently, PCI-32765 is being tested in Phase Ib/II combination with Ofatumumab (NCT01217749), Fludarabine (FA), Cyclophosphamide and Rituximab or Bendamustine and Rituximab (NCT01292135) in CLL patients in the relapsed setting. Data from Phase I/II trials demonstrated that high-risk CLL patients respond equally as well as low-risk patients to PCI-32765. PCI-32765-treated CLL patients characteristically have delayed responses or stable disease due to persistent lymphocytosis, caused by redistribution of tissue-resident CLL cells into the peripheral blood. To accelerate and improve responses and to expand upon the PCI-32765 experience in high-risk CLL patients, Burger *et al.* [32] reported results of an ongoing Phase II study of PCI-32765 plus Rituximab in 40 patients (median age 65 years) with one of the following characteristics, all predictive of poor outcome to standard

chemotherapy: deletion in chromosome 17p, mutation in the tumor suppressor gene TP53, deletion in chromosome 11q or relapse < 36 months after chemo-immunotherapy. Patients were treated with PCI-32765 420 mg daily, in combination with weekly Rituximab (375 mg/m²) for weeks 1–4 (cycle 1), then daily PCI-32765 plus monthly Rituximab until cycle 6, followed by daily single-agent PCI-32765. After a follow-up of 6 months, the ORR was 83%, 38 of 40 patients continue on therapy without disease progression with 95% of all patients and 90% of patients with del17p had not progressed. There was a large and rapid reduction in lymph node and spleen sizes, with 84% of patients (26/31) experiencing more than a 50% decrease in lymph node size. Treatment was well tolerated overall, with grade 3 or grade 4 toxicities infrequent and transient in nature, including febrile neutropenia, anemia, mucositis and pneumonia, in this clinical study.

Brown *et al.* [33] reported the interim results of Phase Ib/II study of a combination study of PCI-32765 with Bendamustine/Rituximab (BR) in patients with R/R CLL. This combination trial enrolled a total of 30 patients in the BR cohort; 37% were refractory (treatment free interval < 12 months) to a purine analog containing regimen and 13% refractory to Bendamustine. At 8.5 months of median follow-up, the ORR with BR was 93%, with 13% of patients achieving a CR with no morphologic evidence of CLL. No new safety signals with the combination of PCI-32765 and BR were identified. The high ORR, rapid onset of response, low rate of progressive disease and good tolerability, compare favorably with historical controls, have prompted a randomized Phase III study of PCI-32765 in combination with Bendamustine/Rituximab.

Jagłowski *et al.* [34] reported the results of a combination of PCI-32765 with Ofatumumab (O), an anti-CD20 monoclonal antibody. Patients with R/R CLL/SLL following 2 therapies were treated with PCI-32765 was first given as a single agent, 420 mg/day, 4 weeks prior to the addition of Ofatumumab on day 1 of cycle 2 (initial dose, 300 mg; 2000 mg on days 8, 15 and 22 of cycle 2, weekly in cycle 3 and day 1 of cycles 5 through 8). Interim data from 27 patients (median age 65 years) with either CLL/SLL (n = 24) or Richter's transformation (RT = 3) underwent at least six cycles of treatment. CLL/ SLL/PLL patients (24/24) achieved PR (100% ORR) within six cycles; two-third RT patients had PR. The majority of AEs were G1/2. Grade 3/4 AEs included anemia, pneumonia, urinary tract infection and hyponatremia (7–11%). PCI-32765 combined with Ofatumumab was well tolerated and highly active (100% ORR) in patients with heavily pre-treated R/R CLL/SLL. Rapid onset of response, low relapse rate and favorable safety profile make this combination worthy of further study.

O'Brien *et al.* [35] reported the interim data on the combination of PCI-32765 with Bendamustine (B)/Rituximab (R) (BR) in 30 patients with R/R CLL (median age = 65 years). BR produced an ORR of 59% in R/R CLL. Thirty-seven percent had purine analog-refractory disease and 13% had Bendamustine-refractory disease. Twenty-three percent of the patients had deletion 17p and 43% had deletion 11q. R/R CLL patients received 420 mg of PCI-32765 daily for 28-day cycles until disease progression. Bendamustine was administered 70 mg/m² on days 1 and 2 combined with Rituximab 375 mg/m² on day 0 for cycle 1 escalating to Rituximab 500 mg/m² for cycles 2–6. Response was evaluated according to IWCLL criteria. Grade 3/4 neutropenia and thrombocytopenia were noted in 47 and 10% of patients, respectively. At a median follow-up of 4.9 months (range 2.7–8.3 months), 16 patients have completed BR and 14 patients were receiving BR. The ORR is 90% (27/30 patients) (CR 10%, PR 80%). Two additional patients achieved a nodal response with residual lymphocytosis. Responses appear independent of high-risk clinical or genomic features. PCI32765, in combination with BR, is highly active. The estimated 11-month PFS is 90%. The high ORR, low rate of PD and good tolerability compares very favorably with historical controls, warranting additional investigation of this combination.

Pharmacylics has initiated a randomized Phase III clinical trial of PCI-32765 in combination with Bendamustine and Rituximab in patients with R/R CLL/SLL. The trial is designed to demonstrate superiority of PCI-32765 *versus* Ofatumumab. The primary endpoint of the study is to demonstrate a clinically significant improvement in PFS in relapsed or refractory CLL/SLL patients. This global study plans to enroll 350 patients. Pharmacylics has also initiated the RESONATETM-17p study, a randomized, Phase II trial using PCI-32765 as a monotherapy in patients who have deletion 17p and who did not respond to or relapsed after at least one prior treatment with chemoimmunotherapy. The primary outcome of the study will be ORR. The key secondary endpoints will be duration of response and other measures of clinical benefit. This study is planned to enroll 111 patients worldwide. In addition, Pharmacylics and Janssen have initiated a pivotal Phase III trial of PCI-32765 in combination with Bendamustine and Rituximab in R/R CLL/SLL patients who received at least one line of prior systemic therapy. The primary endpoint of the study is to demonstrate a clinically significant improvement in PFS *versus* Bendamustine and Rituximab therapy alone. The key secondary endpoints include ORR, overall survival and other measures of clinical benefit.

Ibrutinib/PCI-32765 inhibits > 20 TKs other than BTK at nanomolar concentrations. However, it induces variable cyto-toxicity in CLL cells only at micromolar concentrations at which it has been shown to inhibit almost every TK it was tested against. Its interaction with multiple PTKs would be expected to result in poor intracellular pharmacokinetics due to undesired binding to a large pool of 'competing' kinases leading to reduced occupancy of BTK active site. That is likely the cause for the mg/kg dose levels and > 100 nM plasma concentrations of Ibrutinib/PCI-32765 required for BTK active site occupancy in clinical settings. Furthermore, many of the TKIs it inhibits at nanomolar concentrations, including Lyn and Csk [19], are inhibitory TKIs that counterbalance BTK action. Therefore, its promiscuity would be expected to significantly compromise its net impact on lymphoma/leukemia cell survival.

1.1.3 Anaplastic lymphoma kinase inhibitors—Anaplastic lymphoma kinase (ALK) is a RTK of the insulin receptor superfamily that transmits signals through a number of other important kinases, including PI3K and Janus kinase (JAK) [36].

Anaplastic large cell lymphoma (ALCL) is a rare type of aggressive T-cell lymphoma, comprising between 2.5 and 5% of all NHLs [37]. Approximately 50,000 cases of NHL are diagnosed annually in the US. Expression of ALK fusion proteins resulting from chromosomal translocations involving chromosome band 2p23 is a hallmark of ALCL [38]. The most frequently detected ALCL translocation t(2;5) encodes a nucleophosmin (NPM)-ALK fusion protein with constitutive TK activity, which is clearly implicated in the pathogenesis of approximately 80% of cases of ALCL. ALK protein expression is an independent predictor of survival and serves as a useful biologic marker of a specific disease entity within the spectrum of ALCL [39]. ALK-positive ALCLs are highly responsive to cytotoxic drugs [40]. However, relapses occur and require salvage therapy.

The oncogenic role of the ALK fusion oncogene provides a potential avenue for therapeutic intervention. The development of ALK inhibitors, designed to interfere with ALK signaling, has revolutionized the treatment of lung cancer. Crizotinib (PF-02341066, Xalkori; 3-((*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy)-5-(1-(piperidin-4-yl)-1*H*-pyrazol-4-yl) pyridin-2-amine, Pfizer) is a multitargeted TKI, which was originally developed as an inhibitor of mesenchymal epithelial transition growth factor (c-MET); it is also a potent inhibitor of ALK phosphorylation and signal transduction [40]. Extremely promising Phase II results led to accelerated approval of crizotinib by the FDA for the treatment of patients with late-stage, nonsmall cell lung cancers (NSCLCs) who express the abnormal ALK gene. Crizotinib has

progressed into several Phase III trials and a number of other ALK inhibitors are also in early stages of development.

Several second-generation ALK inhibitors are being studied in the clinic for patients with ALK-rearranged cancers. One of these, LDK378, is more potent and selective than Crizotinib and may overcome acquired resistance to Crizotinib. However, the response rate in ALK-positive NSCLC patients suggests that more potent ALK inhibitors like LDK378 may be useful in patients who relapse while on Crizotinib. ASP3026 (*N*2-[2-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]phenyl]-*N*4-[2-[(1-methylethyl)sulfonyl]phenyl]-1,3,5-triazine-2,4-diamine; Astellas Pharma) is being evaluated in Phase I trials in patients with advanced malignancies, B-cell lymphoma, solid tumors and ALK-positive tumors (NCT01284192). Development of a clinical grade anti-ALK antibody is also under way. Combining an anti-ALK antibody with ALK inhibitors might be more effective than either agent alone.

1.1.4 Inhibitors of the PI3K/AKT/mTOR pathway—The PI3K/AKT/mTOR pathway plays an important role in lymphomagenesis. This system regulates the expression of cyclin D1, c-Myc and STAT3 proteins, which are involved in the pathogenesis of B-cell NHL [41].

1.1.4.1 PI3K inhibitors: Direct inhibition of the lipid kinase PI3K can potentially lead to inhibition of AKT and mTOR, both of which are critical regulators of cell proliferation and growth. Inhibition of PI3K results in apoptosis of DLBCL tumors [42]. Excessive PI3K activity is characteristic in HL. GS-1101 (CAL-101, (*S*)-2-(1-((9*H*-purin-6-yl)amino)propyl)-5-fluoro-3-phenyl-quinazolin-4(3*H*)-one; Calistoga Pharmaceuticals) is a potent PI3K δ inhibitor [43]. In a dose-escalation study in 57 patients (NHL, *n* = 29; CLL, *n* = 18; AML, *n* = 10), 49% with refractory disease, responses were seen at all dose levels with OR in 9 of 15 indolent NHL, 6 of 7 MCL and 14 of 16 CLL had reduced lymphadenopathy accompanied by increasing lymphocytosis [44]. In a Phase I study, CAL-101 showed acceptable safety and promising clinical activity in heavily pretreated patients with CLL [45]. In an ongoing Phase II study, 21 pre-treated patients were treated with the combination of GS-1101 (150 mg BID continuously) and Ofatumumab (300–1000 mg weekly for 7 weeks and monthly for 4 months) [46]. The nodal response rate was high at 85%, and the addition of Ofatumumab resulted in rapid resolution of lymphocytosis, such that the ORR was 80% with 10% CR rate. In both studies, the dose-limiting toxicity was elevation of liver enzymes. The combination regimen is going to be studied further in a Phase III registration trial. A Phase III study is examining GS-1101 in combination with Rituximab in previously treated CLL patients. This study is planned to enroll 160 patients at approximately 70 sites in the US and Europe.

1.1.4.2 AKT inhibitors: AKT is an important kinase downstream of the lipid kinase PI3K that regulates cell survival, cell proliferation and glucose metabolism. Activation of AKT has been described in several cancers including NHL [47].

MK-2206 (8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-1,2,4-triazolo[3,4-*f*][1,6]naphthyridin-3(2*H*)-one hydrochloride; Merck) is an orally selective allosteric inhibitor. A Phase II trial is evaluating safety and efficacy of MK2206 (200 mg PO once weekly on days 1, 8, 15 and 22 on a 28-day cycle) in patients with relapsed or refractory diffuse large B-cell lymphoma (NCT01481129). Perifosine (1,1-dimethylpiperidinium-4-yl octadecyl phosphate; Keryx Biopharmaceuticals) is an oral, synthetic alkylphospholipid, with multiple effects including inhibition of AKT. A Phase II study has evaluated the activity and safety of orally administered Perifosine (150 mg daily for 28 days per cycle) in 36 patients with R/R Waldenstrom macroglobulinemia (WM). In this study, oral Perifosine was well tolerated and with encouraging activity with an ORR of 35 and 54% had stable disease [48].

Gastrointestinal symptoms of some degree occurred in > 65% in the Phase II trial. Although grade 3–4 hematologic toxicity was uncommon, grade 1–2 anemia and neutropenia were seen in 65 and 49%, respectively.

Combination of Perifosine with the multikinase inhibitor Sorafenib (Nexavar, Bayer) induces gene expression profiling and signaling changes resulting in a synergistic cytotoxic activity against lymphoma cell lines. Combination therapy with Perifosine (50 mg BID, per os) and Sorafenib (400 mg BID, per os) was well tolerated in a Phase II study in heavily pre-treated lymphoma patients [49]. Promising clinical response was observed in R/R classical HL (cHL) patients, suggesting this subgroup could represent the target population for future studies. A reduction of phosphorylated extracellular signal-regulated kinase (p-ERK) and p-AKT during the first 2 months of therapy was a significant predictive value of clinical response.

1.1.4. 3 mTOR Kinase inhibitors: The mTOR kinase, an essential mediator of growth signaling that originates from PI3K, exists in two different complexes: mTORC1 and mTORC2. There are currently four mTOR inhibitors in the clinic: Rapamycin (Sirolimus) and the Rapalogs: Temsirolimus, Everolimus and Deforolimus. Temsirolimus and Deforolimus are intravenous (IV) agents, whereas Everolimus and Sirolimus can be administered orally. Rapalogs have improved hydrophilicity and can be used for oral and IV. All of these compounds have demonstrated activity against lymphoma cells both *in vitro* and *in vivo*.

1.1.4.3.1 Everolimus: Treatment of MCL cell lines with Everolimus (RAD001, Novartis) inhibits phosphorylation of mTOR substrates and induces G1 arrest. Everolimus can also sensitize MCL cell lines to a variety of cytotoxic agents, including Doxorubicin and Bortezomib. Similar results have been observed in DLBCL cell lines. Everolimus has single-agent activity in relapsed/ refractory aggressive NHL and provides proof of concept that targeting the mTOR pathway is clinically relevant.

Everolimus has been evaluated in a Phase II trial of patients with relapsed NHL and HL after a median of four prior therapies. Patients received Everolimus (10 mg PO daily) until disease progression or unacceptable toxicity. The ORR in 145 evaluable patients was 33% (5 CRs, 43 PRs). In patients with MCL, the ORR was 32%; in patients with DLBCL, the ORR was 30% and in patients with T-cell lymphoma, the ORR was 63%. In the 48 responders, the median duration of response was 6.8 months [50]. Among the 19 HL patients, the ORR was 47% (1 CR, 8 PRs). The median PFS interval was 6.2 months, median OS time was 25.2 months, and median duration of response in nine responders was 7.1 months [51]. However, 74% patients experienced grade 3/4 toxicity requiring dose reduction. Thus, Everolimus has single-agent activity in relapsed/refractory aggressive NHL and provides proof of concept that targeting the mTOR pathway is clinically relevant.

Zent *et al.* [52] treated 22 patients with CLL/SLL with Everolimus and demonstrated an 18% ORR. A decrease in lymphadenopathy was observed in 36% of patients. Absolute lymphocyte count increased a median of 4.8-fold, concomitant with the clinically measurable lymphadenopathy decreasing a median of 75.5% (range 38–93%) compared with pretreatment measurements. Ghobrial *et al.* [53] reported the results of Everolimus in patients with relapsed WM. Fifty patients were enrolled, and the ORR was 42%. The estimated PFS at 6 and 12 months is 75 and 62%, respectively. The primary toxicity was hematologic with dose reductions in 52% of patients. Pulmonary toxicity occurred in 10% of patients.

A Phase II study of the combination of Everolimus and Rituximab in R/R DLBCL has just been completed (NCT00869999). Preliminary results from a Phase II study in MCL patients refractory to Bortezomib reported promising single-agent activity and good tolerability [54]. Phase I/II studies exploring the novel combinations of Everolimus and Panobinostat (LBH589) [55] or Bortezomib (NCT00671112) are still ongoing.

1.1.4.3.2 Temsirolimus: Temsirolimus (CCI-779/Torisel, Pfizer), a water-soluble ester derivative of Rapamycin, has been evaluated in two Phase II trials in patients with relapsed MCL, and promising response rates up to 40% were found [56,57]. Subsequently, a randomized Phase III trial was initiated in 162 patients with R/R MCL, in which superiority in remission induction and PFS was demonstrated for a regimen of Temsirolimus 175 mg for 3 weeks, followed by a 75-mg weekly administration in comparison with established agents. The most common drug-related AEs were skin toxicity and mucositis/stomatitis. This study found an ORR of 22% with Temsirolimus compared with 2% with the investigators' choice of single agents [58]. The median PFS, which was the endpoint in this study, was longer in the Temsirolimus-treated groups. The median PFS time was 4.8, 3.4 and 1.9 months for the Temsirolimus 175/75, 175/25 and investigators' choice groups, respectively. Those with the higher dose of Temsirolimus had a longer PFS than those treated with the investigators' choice therapy. This study led to the addition of Temsirolimus to the therapeutic armamentarium for the treatment of MCL in Europe. A Phase II study of Temsirolimus plus Rituximab produced a 59% ORR; the most common grade 3 or 4 AE in Rituximab-sensitive and -refractory patients was thrombocytopenia (17 and 38%, respectively) [59]. The mTOR pathway is constitutively activated in DLBCL and Temsirolimus has been shown some activity in DLBCL with an ORR of 28%, a CR of 12% and a median PFS of 2.6 months [60]. In summary, Temsirolimus has modest single-agent activity in relapsed MCL and is a new therapeutic choice for these patients.

1.1.4.3.3 Deforolimus: Deforolimus (AP23573/MK-8669, Ariad Pharmaceuticals) has been tested in a Phase II study in a group of 55 relapsed/refractory patients with different hematological malignancies [61]. Patients received 12.5 mg Deforolimus given IV over 30 min once daily for consecutively 5 days every 2 weeks on a 4-week cycle. The dose was based on results from a Phase I trial evaluating the same dosing schedule [62]. Hematologic improvement/stable disease was observed in 21 (40%). Of the five disease cohorts, the most favorable response was seen among patients with MCL, with three out of nine achieving a PR, which highlights the potential of these drugs in this subtype of NHL.

The mTOR inhibitors Temsirolimus and Everolimus clearly have single-agent activity in NHL, CLL/SLL, HL, and WM and might be successfully combined with other drugs for optimal efficacy. The activity is modest and the drugs are generally well tolerated. A comparative toxicity profile of these compounds showed myelosuppression, skin rash and stomatitis. These agents are now being tested in larger single-agent studies as consolidation after induction therapy for DLBCL, as treatment for new untreated WM, relapsed HL and in combination with chemoimmunotherapy for untreated MCL.

Rapamycin and Rapalogs only block one component of the pathway (mTORC1). Only a subset of the cancers that have mutations in RTK-PI3K-mTOR signaling will respond to mTOR inhibitors. Moreover, the cytostatic effects of Rapalogs in cancers are limited by feedback activation of PI3K, Ras/MAPK, mTORC2 and downstream AGC kinases, all of which oppose Rapalog effects on protein biosynthesis and cell cycle. Thus, mTOR inhibition can actually activate other oncogenic pathways in many contexts. Consequently, newer agents are under development that target both mTORC1 and mTORC2, mTORC1 and PI3K and the triad of PI3K, mTORC1 and mTORC2 without causing hyperglycemia and hyperlipidemia [63].

1.1.5 Src family kinase inhibitors—The Src family kinases (SFKs) are the largest family of nonreceptor TKs (NRTK) and one of the best-studied targets for cancer therapy [64,65].

Dasatinib (Sprycel, BMS-354825; *N*-(2chloro-6-methyl-phenyl)-2-(6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrro-midin-4-ylamino)thiazole-5-carboxamide, Bristol-Myers Squibb) is an ATP-based competitor that was developed as a dual inhibitor of the Src family and Abl TKs (c-Src, Lck, Hck, Yes, Fgr, Lyn and Fyn) that is FDA approved for the treatment of CML. Approximately 95% of CML patients and 30% of acute lymphoblastic leukemia (ALL) patients are positive for the 'Philadelphia chromosome,' a mutation associated with tumors that are often difficult to treat with currently available therapies. Currently, five FDA-approved TKIs are available in the US—Gleevec (Imatinib), Tasigna (Nilotinib), Sprycel (Dasatinib), Bosulif (Bosutinib) and Ponatinib (Iclusig)—for people with CML or Philadelphia chromosome-positive ALL. Imatinib, Dasatinib, Nilotinib and Bosutinib all fail to be effective in patients with the *T315I* mutation. However, patients that express this mutation respond very well to Ponatinib.

Dasatinib is also a potent inhibitor of five other critical oncogenic TK families: SRC, c-KIT, PDGF receptors (α and β), BTK and ephrin (EPH) receptor kinases [66]. William *et al.* [67] reported the preliminary results of a Phase I/II trial on the safety and clinical activity of Dasatinib in NHL. The primary endpoint was MTD of Dasatinib in the Phase I stage and ORR in Phase II stage of the study. Dasatinib showed encouraging activity in heavily pretreated, recurrent or refractory NHL patients. Major toxicities noted were grade 3 pleural effusions and cytopenias. Dasatinib was found to be particularly effective in patients with peripheral T-cell lymphomas (PTCL); possibly because of high expression of PDGFR- α . After two cycles of treatment (150 mg PO 28-day cycles), the ORR was 32%, PFS was 17% at 1 year and 13% at 2 years. Overall survival was 60% at 1 year and 50% at 2 years. The two patients who sustained a CR had PTCL.

1.1.6 Protein Kinase C (PKC) inhibitors—Protein kinase C (PKC) is a family of serine/threonine kinases that regulate a variety of cell functions including proliferation, gene expression, cell cycle, differentiation, cytoskeletal organization, cell migration and apoptosis [68]. Small molecule approaches to inhibiting PKC have been directed toward the ATP-binding site or the diacylglycerol-binding site. Enzastaurin (LY317615, 3-(1-methylindol-3-yl)-4-[1-[1-(pyr-idin-2-ylmethyl)piperidin-4-yl]indol-3-yl]pyrrole-2,5-dione, Eli Lilly & Co.) is an oral serine/threonine inhibitor that suppresses cell signaling through the PKC-/PI3K/AKT pathways [69]. In a Phase II study, Morschhauser *et al.* [70] treated 60 patients with relapsed MCL with 500 mg of Enzastaurin daily. The most common side effect was fatigue. Although there were no documented antitumor responses, 37% remained progression free for > 3 months, and six patients were progression free for 6 months or more. In a Phase II study in R/R DLBCL, prolonged freedom from progression (FFP) was observed with little grade 3 toxicity. Preliminary results from a subsequent study in aggressive NHL also indicate single-agent activity. In a multicenter, Phase II study, Robertson *et al.* [71] treated 55 patients with relapsed or refractory DLBCL with Enzastaurin (500 mg daily) until disease progression or unacceptable toxicity. The primary endpoint was FFP for at least two cycles (2 months), and 22% of patients met this endpoint. The agent was well tolerated and the only grade 4 toxicity observed was hypomagnesemia. These encouraging data led to the initiation of Phase III trials with Enzastaurin in combination with Rituximab plus CHOP chemotherapy in patients with DLBCL (NCT00332202). In a Phase II study in stage III–IV FL patients receiving Enzastaurin 500 mg/d for up to 3 years or until progression, the ORR was 25% [72]. Clinical data with Enzastaurin in SLL/ CLL are quite limited with a single report on seven patients showing an ORR of 14.3% and a median PFS of 10.2 months [73]. The best results with Enzastaurin

have been reported in WM patients [74]. In a Phase II study, 29 previously treated patients were given 500 mg/day Enzastaurin for 8 months or until disease progression. In all, 27.9% of the patients had a measurable response, with a decrease in monoclonal IgM > 25% in 37.9% of these cases.

1.1.7 Ras/Raf/MEK/ERK pathway inhibitors—The Ras/Raf/mitogen-activated kinase 1/2 (MEK1/2)/MAPK pathway is one of the most frequently dysregulated signaling cascades in cancer. Activating mutations of Ras and Raf occur frequently in both solid tumors and hematologic malignancies, leading to activation of their downstream targets MEK1/2 and extracellular signal-regulated kinase (ERK) 1/2. *Ras* mutation rates vary widely in hematopoietic cancers, with values ranging in leukemias from as low as 5% in CML to 27–70% in chronic myelomonocytic leukemia (CMML) [75]. A prevalence of activating mutations of both *K-ras* and *N-ras* has been described in MM [76]. The use of farnesyl transferase inhibitors (FTI) in the treatment of solid tumors has been disappointing despite promising preclinical studies. Unfortunately, the history of FTIs in the treatment of leukemias and lymphomas has also been disappointing [77]. Despite this, some clinical trials for hematopoietic malignancies are still ongoing that focus on the use of FTIs, either as single anti-Ras agents or in combination with different drugs targeting other components of relevant signaling pathways. The nonpepti-domimetic oral FTI, Tipifarnib (Zarnestra, R115777, 6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methylquinolin-2(1*H*)-one; Johnson & Johnson), has been used to treat patients with relapsed DLBCL, grade 3 FL or MCL. Of the 38 patients who were evaluated, 18% had PR and 21% had stable disease [78]. A second study in 11 MCL patients showed only one CR (9%) [79].

The multikinase inhibitor Sorafenib (BAY 43-9006, 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino] phenoxy]-*N*-methyl-pyridine-2-carboxamide; Bayer/Onyx) was initially developed as a Raf-1 inhibitor but has subsequently been shown to inhibit multiple other kinases, including FLT3, PDGFR, VEGFR1 and VEGFR2 [80]. Ongoing clinical trials are testing the usefulness of anti-Ras monoclonal antibodies trial as well as various inhibitors of downstream kinases such as the Raf inhibitor Sorafenib or the MEK inhibitors AS703026 and GSK1120212.

1.1.8 JAK/STAT kinase inhibitors—The Janus kinase (JAK) family comprises cytoplasmic receptor-associated TKs that are involved in signal transduction pathways mediated by many cytokines and cytokine-like hormones [81].

Pacritinib (SB1518, 11-(2-pyrrolidin-1-yl-ethoxy)-14,19-dioxo-5,7,26-triaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8,10,12(27),16,21,23-decaene; Cell Therapeutics) is an orally bioavailable inhibitor of JAK2 and the JAK2 mutant *JAK2V617F* with antineoplastic activity. SB1518 competes with JAK2 for ATP binding, thereby inhibiting JAK2 activation. SB1518 is currently being evaluated in Phase I and I/II clinical trials in the US for treatment of chronic idiopathic MF as well as advanced lymphoid malignancies including malignant HL and B-cell lymphoma and advanced myeloid malignancies including AML, CMML and CML. A Phase I study of SB1518 has provided evidence of activity in patients with relapsed lymphoma. Patients were treated at doses up to 400 mg orally daily [82]. Eighteen patients were enrolled, and three patients at the 300-mg dose level demonstrated disease response (1 FL, 1 SLL and 1 MCL). Eleven patients (73%) had stable disease. The effect of drug treatment on p-JAK2, p-STAT3 and p-STAT5 was examined and SB1518 inhibited the JAK/STAT pathway as early as 4 h after administration.

1.1.9 Aurora kinase inhibitors—The Aurora kinases (AKs) have emerged as particularly promising targets due to their roles in regulating multiple signaling pathways crucial for accurate cell division.

The AKs have shown to be promising drug targets in pre-clinical models and several small molecules targeting Aurora kinases A and B or both have entered the clinic. Alisertib (MLN8237, 4-{{[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-yl]amino}-2-methoxy-benzoic acid; Millennium Pharmaceuticals), a selective, ATP-competitive oral reversible AA inhibitor, is furthest along in the development. The peripheral T-cell lymphomas (PTCLs) are uncommon lymphoid diseases that account for 10–15% of all NHL cases in the US. Compared with B-cell NHLs, the PTCLs are generally aggressive and less responsive to current treatment options. Relapsed and refractory diseases are common. Novel and target therapies are in much need to improve quality and duration of response. In a Phase II trial of Alisertib administered orally twice daily for 7 days on 21-day cycles in patients (*n* = 48) with relapsed aggressive NHL including eight patients with PTCL, the ORR was 32% [83]. Response in T-cell NHL was the most impressive at 57%: four out of eight patients responded, and some of the responses were durable. The ORR in DLBCL and MCL was modest around 20%. Treatment-related side effects were generally tolerable and included low blood counts, fever, fatigue and inflammation in mouth. Based on these results, a Phase III, open-label, multicenter trial is ongoing in patients with relapsed or refractory PTCL who will be randomized to Alisertib or investigator's choice (Pralatrexate, Gemcitabine or Romidepsin) [84]. The primary endpoints are the ORR and PFS. Secondary endpoints include CR and unconfirmed CR, overall survival, time to progression and quality-of-life assessments.

Biomarkers of response are necessary to assess the degree of target inhibition in patients who are treated with aurora kinase inhibitors. Patient selection based on aurora A and/or aurora B overexpression may be a useful strategy to test whether these subpopulations will benefit from therapy with aurora kinase inhibitors. Some histologically aggressive lymphomas, for instance, are known to overexpress the aurora kinase A gene. The mitotic index constitutes a biomarker for Aurora A activity, because inhibition of Aurora A in cancer cells resulted in accumulation in mitosis [85]. Another biomarker for Aurora A activity is the degree of autophosphorylation on threonine at residue 288 (T288) of histone H3 [86]. Biological evidence of Aurora B inhibition is the inhibition of histone H3 phosphorylation on serine 10 [87]. Future studies with AK inhibitors are likely to be in combination with radiotherapy, chemotherapy or other targeted anticancer agents already in use for the treatment of various hematological cancers.

2. Conclusion

Recent advances in B-cell lymphomas have produced information critical to our understanding of cell growth, proliferation and cell death in malignant cells. The intracellular machinery and signaling cascades that are active in maintaining the malignant phenotype in B-cell lymphomas and leukemias have revealed multiple potential targets for new agents that inhibit critical signaling pathways, promote apoptotic mechanisms or modulate the tumor microenvironment. Inhibiting these pathways may result in significant clinical benefit for patients. These advances have spawned several clinical investigations of TKIs targeting the BCR, the PI3K/AKT/mTOR, Src family, Ras/Raf/MEK/ERK, JAK/STAT, and Aurora kinase signaling cascades. The robust antitumor activity and tolerability of newer TKIs seen in multiple clinical trials suggest that single-agent therapy could be effective in selected malignancies and might be successfully combined with other drugs for optimal efficacy against relapsed or refractory lymphomas or leukemias.

3. Expert opinion

The prognosis of patients with relapsed or refractory lymphomas or leukemias is poor. Several novel targeted TKIs have recently emerged as active in the treatment of relapsed or refractory B-cell lymphomas that inhibit critical signaling pathways, promote apoptotic mechanisms or modulate the tumor microenvironment. Although most of these drugs have single-agent activity in various subtypes of B-cell lymphomas, successful development of targeted TKIs is dependent upon identifying reliable molecular and clinical markers associated with clinical benefit. The activity and tolerability of TKIs seen in multiple clinical trials suggest that single-agent therapy could be effective in selected malignancies and might be successfully combined with other drugs for optimal efficacy. We now recognize that molecular heterogeneity exists even within a particular cancer type, and therefore targeted TKIs may only benefit select cohorts of patients. Consequently, biomarker identification should be a focus of development for many new TKIs to overcome redundancy and crosstalk among activated signal transduction pathways responsible for B-cell malignancies. Experience with oncologic agents such as mTOR and ALK inhibitors demonstrates that clinical efficacy may prove elusive if predictive markers of response and/or resistance are not identified.

However, more important long-term safety issues of using TKIs still need to be investigated. Majority of TKIs undergoing clinical development target the conserved ATP-binding site within the catalytic domain of the kinase. Because of the similarities of the ATP pocket structures among different kinases, the ATP-competitive TKIs affecting multiple TKs can have off-target effects that lead to undesirable side effects such as hypertension, myelosuppression, teratogenicity, neutropenia, thrombocytopenia or autoimmune diseases. Moreover, most TKIs are widely distributed in different cell types, inhibiting its catalytic activity bears the risk of unwanted consequences on various physiological functions such as cell differentiation, adhesion and proliferation. ATP-binding site TKIs have the high potential to interact with multiple PTKs, thereby resulting in poor intracellular pharmacokinetics due to undesired binding a large pool of 'competing' kinases leading to reduced occupancy of the targeted TK active site. Therefore, despite their *in vitro* potency, the higher doses required to achieve antitumor activity in clinical settings would be expected to cause dose-limiting toxicity as well as counterbalance the specificity of targeted TK inhibition. Combining inhibitors of different signaling pathways or combining a signaling inhibitor with conventional treatments may have a synergistic, antineoplastic and/or anti-inflammatory effect. Future combinations of these agents should increase overall response rates with decreased toxicities. Further insights into the dynamic networks linking the various signaling pathways will likely inform the design of rationally designed treatment strategies and may ultimately lead to paradigm-shifting, biomarker-guided personalized treatments against malignant lymphoma using specific combinations of kinase inhibitors according to specific schedules.

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Declaration of interest

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Article highlights

- Deregulation or overexpression of specific oncogenic tyrosine kinases contributes to the malignant phenotype in B-cell lymphomas and leukemias.
- Several novel targeted tyrosine kinase inhibitors (TKIs) have recently emerged as active in the treatment of relapsed or refractory B-cell lymphomas that inhibit critical signaling pathways, promote apoptotic mechanisms or modulate the tumor microenvironment.
- Multiple clinical trials have revealed that robust antitumor activity can be obtained with newer TKIs directed toward specific oncogenic TKs that are genetically deregulated in various subtypes of B-cell lymphomas and leukemias.
- Clinical success of targeted TKIs will be dependent upon identifying reliable molecular and clinical markers associated with select cohorts of patients.
- The activity and tolerability of TKIs seen in multiple clinical trials suggest that single-agent therapy could be effective in selected malignancies and might be successfully combined with other drugs for optimal efficacy against lymphoma/leukemia cell survival.

This box summarizes key points contained in this article.

Figure 1. Regulatory network of kinases and their signaling pathways
See text for discussion of kinase inhibitors.

Table 1

Select list of kinase inhibitors currently in clinical development for the treatment of B-cell lymphoid malignancies.

Target kinase and inhibitor(s)	Clinical stage and patient types	Results [Refs.]
SYK inhibitor		
Fostamatinib disodium (R788)	Phase II: R/R B-cell NHL and CLL	ORR: SLL/CLL (55%), DLBCL (22%), MCL (11%) and FL (10%); overall mPFS: 4.2 m [13]
Ibrutinib (PCI-32765)	Phase Ib/II: R/R CLL/SLL, MCL, FL, DLBCL, MM, Indolent NHL, MALT/MZL Phase III: CLL/NHL	ORR: SLL/CLL (79%), MCL (78%), WM (75%), FL (46%), MZL (33%), DLBCL (29%), 7 CRs, 23 PRs; mPFS: 13.6 m [23] ORR: R/R MCL (75%) [25] ORR: R/R MCL (68%); mPFS: 13.9 m [26] ORR: R/R DLBCL (23%) [27] ORR: R/R CLL or SLL (68%), 1-year ePFS: 86% [28] ORR: R/R CLL or TN CLL (81%); ePFS at 18 m (> 80%) [29] ORR: R/R CLL (71%), ePFS at 26 m (75%); TN CLL (68%); ePFS at 26 m (96%) [30]
PCL-32765/Rituximab	R/R CLL/SLL, High-risk CLL	ORR: CLL/SLL (83%); LN reduction (> 50%) [32]
PCL-32765/Bendamustine/Rituximab	R/R CLL/SLL, High-risk CLL	ORR: CLL/SLL (93%) -- 13% CR [33] ORR: R/R CLL/SLL (90%) -- 10% CR, 80% PR; ePFS at 11 m (90%) [35]
PCL-32765/Ofatumumab	R/R CLL/SLL, High-risk CLL	ORR: R/R CLL/SLL (100%) [34]
ALK inhibitors		
ASP3026	Phase I: B-cell lymphoma	Ongoing: safety/tolerability and ORR
PI3K inhibitors		
GS-1101 (CAL-101)	Phase I: Indolent NHL, FL, MZL, DLL	CLL: LN reduction (> 50%), mPFS at 15 m (46%) [45]
GS-1101/Ofatumumab	Phase II: CLL	ORR: CLL (80%) -- 10% CRs; LN reduction (85%) [46]
AKT inhibitors		
Perifosine	Phase II: WM, HL Phase III	ORR: 35 -- 11% PR; stable disease: 54%; mPFS: 12.6 m (WM) [48]
Perifosine/Sorafenib	Phase II: R/R B-cell lymphoma, R/R CHL	PR: 22%; stable disease: 42%; PD: 36%; mPFS: 5 m [49]
mTOR inhibitors		
RAD001 (Everolimus)	Phase I: R/R NHL Phase II: R/R NHL, HL, TCL	ORR: TCL (63%), HL (47%), DLBCL, MCL (32%) [50] ORR: HL (47%); mPFS: 6.2 m [51] ORR: RR CLL/SLL (18%) [52] ORR: 70 -- 42% PR; ePFS at 12 m (62%) [53]
CCI-779 (Temsirolimus)	Phase II: WM Phase II: R/R MCL	ORR: 38 -- 5% CR, 35% PR; TTP: 6 m [57] ORR: 41%; TTP: 6 m [58]
CCI-779 (Temsirolimus)	Phase II: DLBCL	ORR: 28 -- 12% CR; mPFS: 2.6 m [60]
CCI-779/Rituximab	Phase II: R/R MCL	ORR: 59 -- 19% CR; mTTP: 9.7 m [59]
CCI-779/Rituximab	Phase III: R/R MCL	ORR: 22%; mPFS: 4.8 m [58]
AP23573 (Deforolimus)	Phase II: R/R NHL	Response rate: 40% 33% PR (MCL) [62]
Src inhibitors		
Dasatinib (Sprycel, BMS-354825)	Phase I/II: R/R NHL	ORR: 32%; 2-year PFS: 13%; 2-year OS: 50% [67]
PKC inhibitors		
Enzastaurin	Phase II: R/R DLBCL, R or R MCL, FL, CLL/SLL, WM	FFP: R or R MCL (36%) [70]; R/R DLBCL (22%) [71], ORR: FL (25%). IgM decrease (38%) [72]; CLL/SLL (14.3%) [73]
Ras/Raf/MEK/ERK inhibitors		
Tipifarnib (Zarnestra, R115777)	Phase II: Relapsed DLBCL, LF3, MCL	PR: 18%; stable disease: 21%; mPFS: 2 m [78] CR: MCL (9%) [79]

Target kinase and inhibitor(s)	Clinical stage and patient types	Results [Refs.]
JAK/STAT inhibitors		
Pacritinib (SB1518)	Phase I: HL and B-cell lymphoma	Response rate: 14%; stable disease: 73%; mPFS: 3 m [82]
Aurora inhibitors		
Alisertib (MLN8237)	Phase II: Aggressive B- and T-cell NHL	ORR: 32 -- 57% in T-cell NHL, 20% in RR DLBCL and MCL [85]

CLL: Chronic lymphocytic leukemia; CR: Complete response; DLBCL: Diffuse large B-cell lymphoma; DLL: Diffuse large-cell lymphoma; ERK: Extracellular signal-regulated kinase; FFP: Prolonged freedom from progression; FL: Follicular lymphoma; FL3: Grade 3 follicular lymphoma; HL: Hodgkin lymphoma; JAK: Janus kinase; MCL: Mantle cell lymphoma; MEK: Mitogen-activated kinase; MM: Multiple myeloma; ePFS: Estimated progression-free survival; mPFS: Median progression-free survival; mTORL: Mammalian target of rapamycin; NHL: Non-Hodgkin lymphoma; ORR: Overall response rate; PD: Progression of disease; PR: Partial response; R/R: Relapsed or refractory; SD: Stable disease; SLL: Small lymphocytic lymphoma; TTP: Time to progression.