Current Hematologic Malignancy Reports (2019) 14:197–205
https://doi.org/10.1007/s11899-019-00512-0

Targeting BTK in CLL: Beyond Ibrutinib

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Published online: 27 April 2019

Abstract

Purpose of Review While the Bruton's tyrosine kinase inhibitor (BTKi) ibrutinib has revolutionized the treatment of chronic lymphocytic leukemia (CLL), current limitations include off-target toxicities and the development of resistance. In this review, we summarize the emerging data for alternative BTKi.

Recent Findings Second-generation BTKi include acalabrutinib, zanubrutinib, and tirabrutinib which offer greater BTK selectivity. While these agents may limit off-target toxicity, they do not overcome common mechanisms of ibrutinib resistance. Reversible BTKi including vecabrutinib and LOXO-305 inhibit BTK in the presence of C481S mutation, and non-selective reversible BTKi, including ARQ-531, may retain activity despite mutations within *PLCG2*. Early-phase studies are underway to establish the clinical efficacy and toxicity of these agents.

Summary A randomized trial of ibrutinib versus acalabrutinib is ongoing, and acalabrutinib may be an option for ibrutinib-intolerant patients. Results from ongoing trials of alternate BTKi will help to define their role in CLL therapy as single agents or in combination therapy.

Keywords Acalabrutinib · Tirabrutinib · Zanubrutinib · B cell receptor

Introduction

Chronic lymphocytic leukemia (CLL) is clonal disorder arising from autoreactive pre- or post-germinal center B cells with constitutive activation in B cell receptor (BCR) signaling [1–4]. CLL is the most common adult leukemia, disproportionately affecting older adults with a median age of onset of 71 years, and despite an often indolent clinical course and recent advances in treatment, CLL remains a life-limiting illness in the current era with the majority of patients dying due to CLL or clonally related Richter's transformation (RT) [5, 6]. Bruton's tyrosine kinase (BTK) is a key component of proximal BCR signaling. BTK expression is upregulated in CLL cells relative to non-malignant B cells, and targeting BTK in CLL with the irreversible small molecule inhibitor ibrutinib leads to direct cytotoxicity, inhibition of proliferation, disruption in cytokine/chemokine signaling, and inhibition of cell migration [7–10]. In addition to BTK, ibrutinib also inhibits related tyrosine kinases including endothelial growth factor receptor (EGFR), interleukin-2-inducible T cell kinase (ITK), tyrosine kinase expressed in hepatocellular carcinoma (TEC), and bone marrow tyrosine kinase on chromosome X (BMX). While ibrutinib's remarkable clinical activity has transformed the treatment paradigm for CLL, ibrutinib resistance and RT remain a challenge and off-target inhibition appears to mediate important ibrutinib-associated toxicities including increased risk for bleeding and cardiac arrhythmia. Alternative BTK inhibitors (BTKi) are currently in development, and in this review, we will discuss current limitations of ibrutinib, novel BTKi in development, and the emerging evidence from ongoing trials of novel BTKi.

Ibrutinib in CLL

Ibrutinib is a first in class irreversible BTKi approved by the US Food and Drug Administration (FDA) as treatment for relapsed refractory (R/R) or treatment naïve (TN) patients with CLL/small lymphocytic lymphoma (SLL). After encouraging results were noted in CLL patients treated in a phase I study of ibrutinib [11], a phase I/Ib study was conducted in patients with R/R CLL. This study demonstrated unprecedented activity with a 71% overall response rate (ORR) by standard response criteria [12] in a heavily pretreated population,

This article is part of the Topical Collection on *Chronic Lymphocytic Leukemias*

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with an additional 18% of patients experiencing clinical response with ongoing lymphocytosis, termed partial response with persistent lymphocytosis (PRL) [13]. Treatment-emergent lymphocytosis is now recognized as a BTKi class effect resulting from disruption in chemokine signaling between malignant B cells and lymph node stromal cells which typically resolves with treatment; however, prolonged lymphocytosis is seen in a subset of cases and is not associated with adverse prognosis [11, 13–15]. In the subsequent randomized phase III RESONATE trial, ibrutinib was shown to be superior to ofatumumab in patients with R/R CLL/SLL in terms of both progression-free survival (PFS) and overall survival (OS), thus becoming established as a preferred treatment for R/R CLL [16]. Ibrutinib was then studied frontline in a phase Ib/II study of patients age 65 and older with 90% of patients achieving either an objective response or PRL [17]. In the randomized phase III RESONATE-2 trial, treatment with ibrutinib resulted in superior ORR, PFS, and OS compared with chlorambucil in TN CLL patients age 65 and older, and more recently, in the randomized phase III Alliance A041202 trial, ibrutinib or ibrutinib and rituximab (IR) provided superior PFS in comparison with chemo-immunotherapy with bendamustine and rituximab in TN patients aged ≥ 65, and no difference was seen in efficacy between ibrutinib and IR [18••, 19•]. With extended follow-up, responses for TN patients treated with ibrutinib appear to be durable, with 92% of patients remaining progression free at 5 years [20]. Finally, results were recently presented from the randomized phase III ECOG 1912 trial in which patients age 70 and younger without deletion 17p were randomized to either fludarabine, cyclophosphamide, and rituximab or IR with superior PFS and OS seen for patients treated with IR [21]. Thus, ibrutinib is well established as both a frontline and salvage therapy for CLL; however, important limitations with the use of ibrutinib remain.

Resistance to Ibrutinib

Despite the remarkable efficacy of ibrutinib in CLL, disease progression and acquired resistance to treatment occur and overcoming ibrutinib resistance remains an unmet clinical need. Ibrutinib binds to BTK at the cysteine 481 residue (C481) and cysteine to serine mutations (C481S) resulting in impaired BTK binding have been identified as the most frequent means ibrutinib resistance, followed by downstream gain of function mutations within *PLCG2* [22, 23, 24•, 25•, 26, 27]. While C481S and activating mutations in *PLCG2* tend to occur with prolonged treatment, RT represents an alternative means of clonal progression typically occurring within the first 24 months [25•]. Cases of RT appear to result from selection of preexisting disease clones in many cases and are less likely to harbor *BTK* or *PLCG2* mutations [28, 29].

Off-Target Ibrutinib Toxicities

Ibrutinib potently and irreversibly not only inhibits BTK but also inhibits multiple related TEC family kinases, and off-target inhibition appears to contribute to specific ibrutinib toxicities. While some toxicities related to off-target inhibition, for instance, rash and diarrhea related to EGFR inhibition, have a tendency to resolve over time and often do not require dose interruption, other more serious toxicities may limit therapy. In early randomized trials of ibrutinib, increased incidence of atrial fibrillation (AF) was observed in patients treated with ibrutinib relative to control therapies [13, 18••], and subsequently pooled analyses of randomized trials have confirmed increased incidence of AF with ibrutinib [30–32] with a relative risk as high as 4 and incidence greater than 10% after at least 2 years of follow-up in some series [30]. More recently, reports have emerged suggesting an association between ventricular arrhythmia (VA) and ibrutinib therapy [33–38]. Ibrutinib-associated VA appears to be rare; recent analysis of FDA post marketing claims and published literature identified 33 total cases of VA in patients taking ibrutinib including 8 cases with ibrutinib causality considered probable [34]; however, given the morbidity and mortality associated with VA, this remains a serious concern, and sudden cardiac death due to VA may not be recognized or reported making the scope of this risk difficult to quantify. The mechanism of ibrutinib-associated arrhythmia is not well established; while cardiac tissue does express both BTK and TEC [39], it is unclear whether inhibition of these or other off-target kinases results in risk for arrhythmia.

Another ibrutinib-associated toxicity which emerged in early clinical trials is increased risk for bleeding [16, 40], with serious bleeding episodes observed in patients on warfarin or aspirin, leading to prohibition of warfarin in subsequent prospective trials. Analyses of published trial results have confirmed increased rates of bleeding events in patients treated with ibrutinib compared with control arms, although incidence of major bleeding events have not been found to be increased [41, 42]. Both BTK and TEC mediate platelet aggregation via downstream collagen receptor glycoprotein VI (GPVI) signaling [43, 44]. However, patients with X-linked agammaglobulinemia (XLA), an immunodeficiency syndrome defined by absence of BTK activity, do not exhibit an increased bleeding tendency, implying that BTK inhibition is unlikely to be the sole explanation for increased bleeding associated with ibrutinib. Ex vivo studies demonstrate that ibrutinib inhibits platelet aggregation in samples obtained from patients with XLA, and inhibition in GPVI signaling is seen ex vivo in platelet rich plasma obtained from patients receiving ibrutinib but not acalabrutinib, supporting the hypothesis that off-target inhibition contributes to the increased bleeding tendency in patients treated with ibrutinib [45]. Thus, off-target toxicities associated with ibrutinib represent a

current limitation, which is of particular concern given the need for indefinite therapy. Alternative BTKi with greater selectivity, if found to be equally effective, would represent an attractive option for therapy.

Alternative Irreversible BTK Inhibitors

Alternate BTKi which act irreversibly through covalent bond formulation at C481 of BTK have been identified with greater selectivity for BTK relative to other TEC family kinases. While studies of the selective second-generation BTKi spebrutinib did not demonstrate similar efficacy to that seen with ibrutinib [46, 47], other selective BTKi have subsequently shown more promising clinical activity.

Acalabrutinib

Acalabrutinib (Calquence; Astra Zeneca, Cambridge, UK) is a second-generation covalent BTKi FDA approved for treatment of R/R mantle cell lymphoma (MCL) (Characteristics of novel BTKi in Table 1). Acalabrutinib potently and irreversibly inhibits BTK in vitro and in vivo, while displaying significantly less off-target inhibition of other TEC family kinases including EGFR and ITK [48••, 49, 50]. In a phase I/II study of acalabrutinib in patients with relapsed CLL/SLL (ACE-CL-001), a dose of 100 mg oral twice daily was established as achieving ≥97% BTK occupancy at steady state dosing and was selected for the dose expansion cohort [48••]. Observed adverse events (AE) of any grade included headache in 43% of patients, diarrhea in 39%, weight gain in 26%, hypertension in 20%, and nausea in 20%. Grade 3/4 toxicities were uncommon and included hypertension (7%), pyrexia (3%), fatigue (3%), diarrhea (2%), and arthralgia (2%) with no major bleeding, although petechiae occurred in 16% and contusion in 18% of patients. The ORR (including PRL) for the first 60 patients treated on study was 95% at a median follow-up of 14 months with one case of progression with associated C481S mutation. Updated results were subsequently reported, with 134 patients treated with a median follow-up of 20 months. The ORR (including PRL) was 93% with a median PFS not reached [51]. The toxicity profile in the entire cohort was similar to the initial report; however, AF did occur in 3% of patients. In addition to the relapsed cohort, an additional cohort of treatment naïve (TN) patients was enrolled to ACE-CL-001 and results were recently reported. Ninety-nine patients were enrolled, with baseline characteristics including a median age of 64, *IGHV*-unmutated disease in 62%, and del17p in 10% of patients [52]. The ORR in this previously untreated cohort was 97% with 24-month event-free survival estimated at 95% and 36-month PFS of 98%. Only one case of CLL progression was reported at a median follow-up of 33 months. AEs of any grade were similar to prior studies and included diarrhea in 47%, headache in 44%, contusion in 34%, and weight gain in 30%. Grade ≥3 AEs included neutropenia (7%), diarrhea (5%), and headache (5%). AF occurred in 6% of patients (1% grade 3), and hypertension occurred in 14% including 3% grade 3 or greater. Three patients discontinued treatment due to second malignancies, including glioblastoma multiforme, angiosarcoma, and small cell lung cancer. While patients with CLL are known to be at an increased risk for second cancers [53–56], whether BTKi impact the risk for second cancers overall or specific second cancer subtypes is not established and warrants further study including reporting of second cancers in future prospective studies of BTKi. Results from a separate single-center study of acalabrutinib for treatment of patients with either relapsed or TN CLL/SLL were recently reported, with an ORR of 90% in 46 patients with a median PFS not reached at median follow-up of 20 months [57]. The most frequent AEs of any grade again included headache (63%), contusion (50%), and diarrhea (43%), with rash reported in 28% and arthralgia and myalgia occurring in 33% and 26% of patients respectively. BTK occupancy was assessed both in peripheral blood and in lymph node biopsies performed at trough time points after 3 days of dosing and demonstrated 98% lymph node and peripheral blood occupancy with twice daily dosing. Given the increased specificity for BTK relative to ibrutinib, acalabrutinib may be an attractive option for patients intolerant to ibrutinib due to off-target toxicities. Results from 33 patients included in the ACE-CL-001 trial who were

Table 1 Characteristics of novel BTK inhibitors in development for treatment of CLL

BTK inhibitor	BTK binding mechanism	Selectivity for BTK	Relevant non-BTK targets	Phase of clinical development
Acalabrutinib	Covalent, irreversible	High	N/A	II/III
Zanubrutinib	Covalent, irreversible	Moderate	N/A	II/III
Tirabrutinib	Covalent, irreversible	High	N/A	I/II
Vecabrutinib	Non-covalent, reversible	Moderate	ITK	I/II
LOXO-305	Non-covalent, reversible	High	N/A	I
ARQ-531	Non-covalent, reversible	Low	LYN, MEK1	I

BTK Bruton's tyrosine kinase, *CLL* chronic lymphocytic leukemia, *ITK* interleukin-2-inducible T cell kinase, *LYN* Lck/Yes novel tyrosine kinase, *MEK1* mitogen-activated protein kinase kinase 1

previously intolerant to ibrutinib were presented with an ORR (including PRL) of 76% and discontinuation of acalabrutinib required due to AEs in only 6% of patients [58]. A prospective study of acalabrutinib in patients with CLL intolerant to ibrutinib is ongoing (NCT02717611) to confirm the safety and efficacy of acalabrutinib in this patient population. While patients intolerant to ibrutinib may tolerate acalabrutinib, a direct comparison of both toxicity and efficacy of both agents is currently lacking, and results from a phase III head to head study of acalabrutinib versus ibrutinib (NCT02477696) are eagerly anticipated in order to directly compare these two active agents (Table 2). In summary, results to date demonstrate that acalabrutinib is highly active as both a frontline and salvage therapy for CLL. Ongoing prospective studies will help to better evaluate the role of acalabrutinib as a single agent and in combination therapy in CLL, and acalabrutinib is an alternative active agent which may be an option for patients intolerant to ibrutinib due to off-target toxicities or patients at high risk for ibrutinib-associated cardiac toxicities.

Zanubrutinib

Zanubrutinib (formerly BGB-3111, BeiGene, Beijing, CN) is a second-generation irreversible BTKi. In comparison to ibrutinib, zanubrutinib displays greater selectivity for BTK relative to ITK resulting in less inhibition of antigen-dependent cell mediated cytotoxicity in vitro [59] but demonstrates less global kinase selectivity for BTK in comparison to acalabrutinib or tirabrutinib [60]. In a phase I study of zanubrutinib in patients with R/R B cell malignancies including CLL, a recommended phase 2 dose (RP2D) of 320 mg daily (either daily or divided in twice daily dosing) was established as achieving complete peripheral blood BTK occupancy, and with twice daily dosing, the median nodal BTK occupancy at trough concentrations was 99.5% with 94% of patients achieving > 90% nodal BTK occupancy [61]. AEs of any grade observed with treatment included petechiae or bruising (38%), diarrhea (28%), and fatigue (24%), with three serious AEs reported including grade 2 pleural effusion, grade 2 heart failure, and grade 3 purpura. One case of AF (grade 2) was reported. Among patients with CLL/SLL, the ORR (including PRL) was 90% with no cases of disease progression at a median follow-up of 7.5 months. Further studies are ongoing of zanubrutinib as a single agent or as part of combination therapy (Table 2) to further assess the safety and efficacy of this therapy for CLL and other B cell malignancies.

Tirabrutinib

Tirabrutinib (formerly ONO/GS-4059, Ono Pharmaceutical, Osaka, Japan) is a potent and selective second-generation covalent irreversible BTKi, which similar to acalabrutinib demonstrates a high degree of selectivity for BTK relative to other

Table 2 Ongoing studies of novel BTK inhibitors in CLL

Drug	Trial identifier	Phase of study	Patient population	Comparator	Combination partner
Acalabrutinib	NCT0217611	II	R/R (ibrutinib intolerant)	N/A	N/A
	NCT02717611	III	R/R	Ibrutinib	N/A
	NCT02457598	III	TN	Obinutuzumab + chlorambucil	Single agent or + obinutuzumab
	NCT02970318	III	R/R	R-idelalisib or BR	N/A
	NCT02296918	II	TN and R/R	N/A	+ Obinutuzumab, + venetoclax and rituximab, + obinutuzumab and venetoclax
	NCT03580928	II	TN	N/A	+ Obinutuzumab and venetoclax
	NCT03516617	II	TN (early intervention)	N/A	± Obinutuzumab
	NCT03328273	I/II	R/R	N/A	AZD-6738
Zanubrutinib	NCT03734016	III	R/R	Ibrutinib	N/A
	NCT03336333	III	TN	BR	+ BR
	NCT02795182	II	R/R	N/A	+ BGB-A317
Tirabrutinib	NCT02983617, NCT02457598	II	R/R	N/A	+ Entospletinib, ± obinutuzumab
	NCT02968563, NCT02457598	II	R/R	N/A	+ Idelalisib, ± obinutuzumab
Vecabrutinib	NCT03037645	I	R/R	N/A	N/A
LOXO-305	NCT03740529	I	R/R	N/A	N/A
ARQ-531	NCT03162536	I	R/R	N/A	N/A

BTK Bruton's tyrosine kinase, *CLL* chronic lymphocytic leukemia, *R/R* relapsed/refractory, *TN* treatment naïve, *BR* bendamustine and rituximab, *N/A* not applicable

TEC family kinases [60, 62]. In a phase I study of tirabrutinib in patients with R/R B cell malignancies, no maximally tolerated dose (MTD) was reached for the cohort of patients with CLL/SLL at doses up to 600 mg once daily or 300 mg twice daily, and responses were seen across all dose levels [62]. AEs of any grade in the entire cohort of 90 patients included anemia (32%), thrombocytopenia (18%), diarrhea (18%), petechiae (14%), and rash (18%), with one grade 3 hematoma in a patient with CLL occurring during treatment and one case of AF occurring during hospitalization for pneumonia. Among patients with CLL/SLL treated across all dose levels, the ORR was 96% with two cases of progression noted at a median follow-up of 18 months, including one patient with early progression with presumed RT. Four patients discontinued treatment due to AEs including purpura and the previously referenced grade 3 bleeding event (psoas muscle hematoma). Further study of tirabrutinib in combination with other targeted therapies is ongoing (Table 2). While the incidence of toxicities with tirabrutinib compares favorably with studies of ibrutinib, randomized prospective studies are needed to directly compare efficacy and safety in order to establish the role of tirabrutinib as therapy for CLL and other B cell malignancies.

Reversible BTK Inhibitors

While alternative second-generation irreversible BTKi offer greater BTK selectivity, these agents all rely upon covalent binding at C481 rendering them, like ibrutinib, susceptible to resistance via C481S mutation. A novel class of compounds have been characterized which inhibit BTK through non-covalent binding and do not rely upon interaction with C481 [63•]. While these compounds inhibit BTK reversibly rather than irreversibly, in preclinical models, reversible BTK inhibition effectively blocks downstream BCR signaling resulting in cytotoxicity and inhibition of proliferation. Given predicted activity regardless of C481S mutations, this class of agents represents a promising treatment for patients with ibrutinib resistance due to C481S mutations or in patients at risk for resistance prior to the development of dominant C481S clones. Clinical studies of these agents are in early stages, and whether this class of compounds is an effective treatment for B cell malignancies remains to be seen.

GDC-0853

GDC-0853 (Genentech, South San Francisco, CA, USA) is a highly selective reversible BTKi with a distinct BTK binding configuration relative to ibrutinib [64] currently in development for the treatment of auto-immune disease. In preclinical CLL models, GDC-0853 effectively inhibits downstream BCR signaling resulting in downregulation of NF-κB signaling, inhibition of cell proliferation and migration, and direct cytotoxicity, with retained efficacy in C481S-mutated disease including in primary patient samples [64, 65]. While a phase I study of GDC-0853 in patients with R/R B cell malignancies was halted prior to completion of planned enrollment in order to focus development of GDC-0853 on the treatment of autoimmune disease, the results from this study provide a glimpse into the potential efficacy and toxicities of this class of agents. A total of 24 patients were enrolled into this first in human phase I study and treated at doses of 100 mg, 200 mg, or 400 mg [66]. No dose-limiting toxicities (DLT) were noted, and the MTD was not reached prior to study closure; all patients enrolled on study at cessation of enrollment were allowed to escalate to the highest tested dose of 400 mg daily. Observed AEs of any grade included fatigue (38%), nausea (33%), diarrhea (29%), thrombocytopenia (25%), and headache (21%), with grade 3 anemia reported in 13% of patients. Two deaths occurred during study due to influenza and two grade 3 bleeding events occurred, both gastrointestinal bleeding in the setting of non-steroid anti-inflammatory use. While direct assessment of BTK occupancy could not be performed due to the reversible nature of BTK binding, plasma CCL3 levels were assessed as a surrogate for BTK inhibition and were found to decrease following treatment in the CLL cohort, albeit to a lesser degree than that seen in prior trials of ibrutinib. In terms of efficacy, 1 complete response was observed in a patient with MCL and 7 of 14 patients with CLL achieved an objective response (PR or PRL) to therapy, including 1 of 5 heavily pretreated patients with CLL with known C481S mutation, with a mean duration of response of 3.8 months in all responding patients and 2.5 months in patients with CLL. As the study was not able to reach the MTD which may have provided greater BTK inhibition, these results including the relatively short duration of response should be interpreted with caution and further study of alternative agents in this class are needed, but this study provides proof of principal of clinical activity with reversible non-covalent BTKi.

Vecabrutinib

Vecabrutinib (formerly SNS-062, Sunesis Pharmaceuticals, South San Francisco, CA, USA) is a potent reversible inhibitor of BTK and ITK currently in clinical development for the treatment of B cell malignancies. Vecabrutinib, unlike ibrutinib, does not exhibit significant inhibition of EGFR, and due to the non-covalent binding mechanism, vecabrutinib inhibits BTK in vitro in the presence of C481S mutations [67, 68]. Ibrutinib inhibits ITK [69] which is thought to mediate differences in absolute T cell number, ratio of regulatory T cell to total CD4 cells, and proportion of Th17 cells in CLL patients treated with ibrutinib relative to those treated with acalabrutinib [70]. While it is unclear to what extent these ITK-mediated immunomodulatory properties contribute to the efficacy of ibrutinib,

vecabrutinib is expected to share these properties while avoiding EGFR-mediated toxicities such as rash and diarrhea. A first-in-human phase I study was completed in healthy participants to establish the pharmacokinetics of vecabrutinib [71], and a phase Ib study (Table 2) is currently ongoing in patients with R/R B cell malignancies including CLL to establish the MTD and assess preliminary single agent activity, including in patients with C481S mutation.

LOXO-305

LOXO-305 (Loxo Oncology, Stamford, CT, USA) has recently been characterized as a selective, reversible, non-covalent BTKi [72]. Preclinical testing to establish the pharmacokinetics of the drug demonstrates achievable plasma concentrations predicted to provide > 90% BTK occupancy. A phase I/II trial is underway to establish the MTD in patients with R/R B cell malignancies, and a dose expansion cohort is planned for CLL patients with progression following or intolerance to standard therapies to provide preliminary clinical efficacy data.

ARQ-531

ARQ-531 (ArQule, Inc., Woburn, MA, USA) is a reversible BTKi designed to occupy the ATP binding region within the kinase domain of BTK without interaction with C481. In addition to inhibiting BTK, ARQ-531 also inhibits kinases involved in both proximal and downstream BCR signaling (Fig. 1) including the SRC family kinase LYN and the immediate upstream kinase of ERK and MEK1 [73•]. Preclinical work established that ARQ-531 is cytotoxic to CLL cells and inhibits migration and prolongs survival compared with ibrutinib in the Eμ-TCL1 murine CLL model and Eμ-MYC/TCL1 murine model of RT from CLL, suggesting an advantage to reversible inhibition at multiple points within the BCR signaling pathway [73•]. In preclinical models, ARQ-531 retains efficacy in the presence of C481S mutation and also effectively inhibits downstream BCR signaling in cell lines and patient samples harboring activating mutations with *PLCγ2*, presumably through downstream MEK1 inhibition and inhibition of the SRC family kinase LYN interfering with SYK mediated PLCγ2 activation. A phase I dose escalation study (Table 2) is underway in patients with R/R CLL or B cell non-Hodgkin's lymphoma to establish the MTD and RP2D and determine the safety and toxicity profile of ARQ-531. Preliminary results were recently reported from the first 16 patients treated at dose levels up to 30 mg daily [74]. Reported AEs included diarrhea, nausea and vomiting, facial paralysis, and hypernatremia all reported in one patient. Grade 3 AEs included lipase elevation and thrombocytopenia noted in one patient each. CCL3 levels decreased significantly with treatment indicating on-target BTK inhibition, and stable disease was noted in 5 of the 12 evaluable patients including 3 patients with > 25% reduction in tumor measurement on

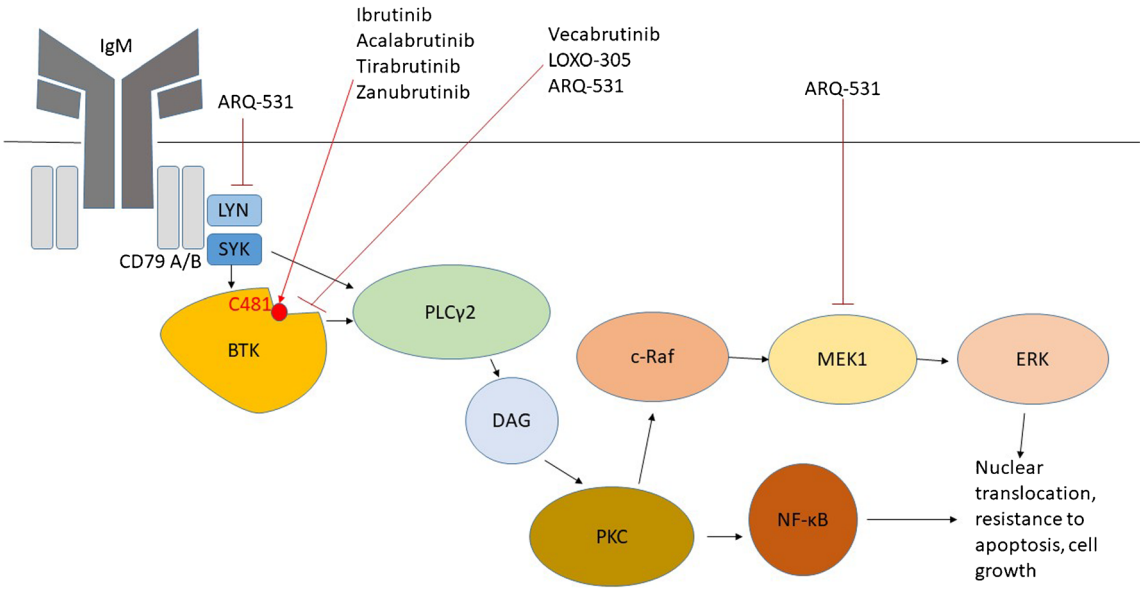

Fig. 1 B cell receptor signaling. This figure depicts a simplified schematic of B cell receptor signaling with targets of select BTK inhibitors. Upon ligation of the B cell receptor, CD79A and CD79B recruit SYK and SRC family kinases including LYN which then recruit BTK and related scaffolding proteins resulting in BTK phosphorylation. BTK and SYK mediate PLCγ2 phosphorylation leading to downstream activation of both ERK and NF-κB signaling. Ibrutinib, acalabrutinib, tirabrutinib, and zanubrutinib bind irreversibly to C481 within the ATP binding site and inhibit BTK phosphorylation. Vecabrutinib, LOXO-305, and ARQ-531 reversibly inhibit BTK phosphorylation via non-covalent binding independent of C481. In addition to inhibition of BTK, ARQ-531 also targets the SRC family kinase LYN as well as MEK1, thereby inhibiting downstream ERK signaling. LYN Lck/Yes novel tyrosine kinase, SYK spleen tyrosine kinase, BTK Bruton's tyrosine kinase, PLCγ2 phospholipase C gamma 2, DAG diacyl-glycerol, PKC protein kinase C, MEK1 mitogen-activated protein kinase kinase 1, ERK extracellular signal-related kinase, NF-κB nuclear factor kappa B

imaging; however, no objective responses had been achieved at the time of preliminary presentation with follow-up currently ongoing.

Conclusions

The success of ibrutinib in the treatment of CLL is difficult to overstate in both TN and previously treated patients; however, there are important limitations to the use of ibrutinib including off-target toxicities and resistance to therapy. Second-generation irreversible BTKi including acalabrutinib offer improved BTK selectivity and are an emerging option for patients intolerant to ibrutinib due to off-target toxicities. Differences in efficacy and toxicity profile have been difficult to compare between ibrutinib and alternative second-generation BTKi, but ongoing head-to-head phase III trials versus ibrutinib will provide much needed data in this regard. Combination strategies are under investigation to improve depth of response to BTKi and more selective irreversible BTKi may be attractive in this setting due to differences in toxicity profile and less predicted inhibition of antibody-dependent cell-mediated cytotoxicity when given in combination with monoclonal antibodies. Finally, reversible BTKi are capable of overcoming the most common mechanism of ibrutinib resistance in preclinical models and are entering into early-phase clinical trials. These agents offer the potential to treat or prevent ibrutinib resistance, and if preclinical results translate into clinical activity, this class of BTKi will represent another step forward in the treatment of CLL.

Compliance with Ethical Standards

Conflict of Interest Jennifer A. Woyach reports grants and personal fees from Janssen, Pharmacyclics, and grants from Abbvie, Loxo, Morphosys, and Karyopharm outside the submitted work. David A. Bond declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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