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New and emerging Bruton tyrosine kinase inhibitors for treating mantle cell lymphoma – where do they fit in?

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Abstract

Introduction: Despite recent prognostic improvements, mantle cell lymphoma (MCL) remains incurable. Bruton tyrosine kinase (BTK) is a key receptor in B-cell tumorigenesis, and the benefits of the first BTK inhibitor, ibrutinib, are becoming clear in MCL. However, off-target activities, which contribute to ibrutinib-related adverse events, suggest potential for further improvement of this drug class.

Areas covered: The authors systematically interrogated ClinicalTrials.gov for trials containing keywords for BTK and MCL. Published literature for new and emerging BTK inhibitors being investigated in MCL was then identified (PubMed and Embase), summarized, and placed in the context of treatment guidelines.

Expert commentary: Reduced off-target effects of new and emerging covalent, irreversible BTK inhibitors under investigation in patients with MCL offer the potential of improved safety compared with ibrutinib. Efficacy may also be favorable based on trial data for acalabrutinib, which has just been approved in the USA as second-line therapy for MCL. The role of BTK inhibitors in treating MCL will evolve substantially over the coming years as results from a number of trials become available, particularly in relation to potential upfront use and possible synergy with other targeted therapies such as B-cell lymphoma 2, phosphoinositide 3-kinase and checkpoint inhibitors.

Keywords: Bruton tyrosine kinase inhibitors; B-cell malignancies; mantle cell lymphoma; efficacy; adverse events; treatment guidelines
1. Introduction

Mantle cell lymphoma (MCL) is classified by the World Health Organization as a B-cell neoplasm with morphological variants of diverse clinical behavior [1]. It is an uncommon malignancy, accounting for around 6% of non-Hodgkin lymphoma (NHL) cases [2]. The incidence of MCL appears to be increasing [3,4], although this may be due to improved diagnosis rather than an increase in the actual frequency of the disease. MCL most commonly occurs in men, with a median age at diagnosis of 68 years [4]. Data support the presence of familial risk factors [5-8] and some environmental risk factors for MCL [6,9], but many associations with environmental factors seen for other NHL types have not been observed for MCL [6]. Survival and relapse rates for MCL have recently improved with the incorporation of novel agents and aggressive upfront therapeutic strategies [10,11]. However, with the possible exception of allograft, MCL is still incurable [12] and a substantial unmet need therefore remains.

Bruton tyrosine kinase (BTK) is a kinase enzyme in the B-cell receptor pathway that is critical for the initiation, survival and progression of B-cell malignancies [13-15]. The unique structure of BTK, which is characterized by a cysteine (Cys-481) within the ATP-binding pocket, has made it an attractive therapeutic target. The first realization of this potential has already materialized with the development of ibrutinib. This first-in-class, irreversible, small-molecule inhibitor of BTK covalently binds to Cys-481 [16] and is indicated for use as second-line therapy in MCL in both the USA (in patients who have received at least one prior therapy) and Europe (in relapsed or refractory disease), based on the positive results of a pivotal phase 2 trial [17,18]. Not surprisingly, numerous additional indications are also being sought for this drug in patients with MCL, including as front-line medication in combination with bendamustine plus rituximab (BR) (NCT01776840).

The clinical benefits of ibrutinib in MCL and other B-cell malignancies are becoming increasingly clear. Nevertheless, the development of additional BTK inhibitors for this disease is warranted owing to off-target inhibition of kinases by ibrutinib [16] that may contribute to the adverse events (AEs) associated with this molecule. These include atrial fibrillation, bleeding, diarrhea, rash, headache and nausea [19-23].
Indeed, data from patients with chronic lymphocytic leukemia (CLL) taking ibrutinib show that AEs are a common reason for treatment discontinuation [24,25]. The state of emerging BTK inhibitors and their implications for the future treatment of B-cell malignancies has recently been reviewed [26]. Here we focus on new and emerging BTK inhibitors that are specifically under investigation in patients with MCL and discuss their potential placement in MCL treatment guidelines.

2. Materials and methods

Searches were conducted on 15 August 2017 in ClinicalTrials.gov to identify trials with fields containing key terms for BTK inhibitors (BTK OR Bruton OR Bruton’s OR Brutons) AND MCL (MCL OR mantle). Filters were applied to exclude studies that had been terminated or withdrawn. It is possible that clinical trials not specifically mentioning MCL in either the ‘condition’ or ‘submitted keywords’ fields in ClinicalTrials.gov may include patients with MCL as part of a broader clinical trial population. However, for the purpose of focusing this review, we considered an absence of MCL search terms to indicate a lack of intent by the investigator and/or manufacturer to move forward into MCL with their molecule. Searches were performed in PubMed (for full papers) and Embase (for conference abstracts) on 21 September 2017 to identify primary research articles with information on new and emerging BTK inhibitor molecules identified from the ClinicalTrials.gov searches. The ‘hits’ from these searches were screened to exclude those with irrelevant study topics and study types (e.g. reviews).

3. New and emerging BTK inhibitors in MCL

In total, 36 trials were identified on ClinicalTrials.gov that included search terms for BTK inhibitors and MCL. Of these, five were excluded because search terms were present in the introductory text but were not the focus of the clinical trial, and 21 were excluded because they were investigating ibrutinib as the only BTK inhibitor. The remaining 10 trials were confirmed as assessing new and emerging BTK inhibitor molecules (acalabrutinib [ACP-196], zanubrutinib [BGB-3111], SNS-062, ARQ-531, M7583 and CT-1530). Details of the ongoing clinical trials identified for the new and emerging BTK inhibitors under investigation in MCL are provided in Table 1. Data identified from the targeted literature searches for each of these molecules are
summarized below, with the exception of CT-1530 for which no published articles (full papers or conference abstracts) were identified.

3.1. Acalabrutinib (ACP-196)

Acalabrutinib inhibits BTK by covalently and irreversibly binding to Cys-481. The IC₅₀ value (concentration where the response is reduced by half) for acalabrutinib against purified BTK is 5.1 nM compared with 1.5 nM for ibrutinib [27]. In cellular assays, EC₅₀ values (concentration that gives the half-maximal response) for acalabrutinib and ibrutinib for inhibition of B-cell receptor (BCR)-induced CD69 expression are 2.9 nM and 0.58 nM, respectively, in peripheral blood mononuclear cells, with comparable results in human whole blood (9.2 nM and 5.8 nM, respectively) [27]. The degree of inhibition of BCR-induced responses (BTK, S6 and ERK phosphorylation) is also similar for these molecules in primary CLL cells [28]. In mice, the ED₅₀ value (dose where the measured effect occurs in at least 50% of samples) for inhibition of CD69 expression in splenocytes was 1.3 mg/kg for acalabrutinib and 2.9 mg/kg for ibrutinib [27]. Pre-clinical anti-tumor effects have been demonstrated for acalabrutinib in terms of reduced cell viability in large B-cell lymphoma cell lines [29], induction of apoptosis in primary CLL cells [28,30] and improved outcomes in a canine B-cell NHL model and two mouse CLL models [31,32]. In healthy volunteers acalabrutinib is rapidly absorbed (Tₘₐₓ [time to maximum plasma concentration of drug] of 0.5–1.0 hours), has a short half-life (T½ [time required for elimination of 50% of drug from plasma] of 0.88–2.1 hours), and reaches full target occupancy with a single 100 mg dose [27]. Robust response rates have been reported with acalabrutinib in a phase 1/2 clinical trial in both relapsed or refractory and untreated patients with CLL (NCT02029443) [33,34]. In this trial, the highest rate of BTK occupancy (98%) was observed with twice-daily dosing [34].

Acalabrutinib has fewer off-target effects than ibrutinib. In a panel of 395 non-mutant kinases, 1.5% were inhibited by at least 65% by 1 μM acalabrutinib, compared with 8.9% for 1 μM ibrutinib [27]. Acalabrutinib also has much lower activity than ibrutinib against kinases with a cysteine in the same position as BTK (TEC family kinases [ITK, TXK, BMX, TEC], EGFR, ERBB2, ERBB4, JAK3 and BLK) and SRC family kinases (FGR, FYN, HCK, LCK, LYN, SRC and YES1) [27]. Indeed, IC₅₀ values for acalabrutinib were below 1000 nM (1 μM) for only four kinases other than
BTK (ERBB4 [16 nM], BMX [46 nM], TEC [126 nM] and TKX [368 nM]), all of which had substantially lower IC₅₀ values in relation to ibrutinib (ERBB4 [3.4 nM], BMX [0.8 nM], TEC [10.0 nM] and TXK [2.0 nM]) [27]. Ibrutinib has been shown to also inhibit SRC, LCK and ITK far more potently than acalabrutinib in healthy T cells [28].

No cases of atrial fibrillation have been observed so far in the phase 1/2 clinical trial of acalabrutinib in the 61 patients with relapsed or refractory CLL, after a median follow-up period of 14.3 months (NCT02029443) [33]. Although rates of atrial fibrillation in this study would be influenced by the exclusion of patients with significant cardiovascular disease and electrocardiogram abnormalities, significant cardiovascular disease was also an exclusion criterion in an ibrutinib trial where cases of atrial fibrillation occurred in 10 out of 195 patients (5%) with relapsed or refractory CLL after a median follow-up of 9.4 months, of which six cases (3%) were grade 3 or higher (NCT01578707) [21]. In another trial in patients with relapsed or refractory CLL, where the presence of electrocardiogram abnormalities was an exclusion criterion, atrial fibrillation was reported as a serious AE in 3 (4%) of 85 patients (median follow-up: 20.9 months) (NCT01105247) [35]. In the phase 1/2 trial of acalabrutinib in CLL there have been no cases of atrial fibrillation with acalabrutinib treatment in the 72 patients with treatment-naïve CLL, at a median follow-up of 11 months (NCT02029443) [34]. In a trial of 136 patients with treatment-naïve CLL receiving ibrutinib, 8 (6%) developed atrial fibrillation (1% were grade 3 or higher) at a median follow-up of 17.4 months [36]. Both studies excluded patients with significant cardiovascular disease [34,36].

No cases of major hemorrhage have been reported in the phase 1/2 clinical trial of acalabrutinib in patients with relapsed or refractory (n = 61) or treatment naïve CLL (n = 72) (NCT02029443) [33,34], with the exception of a single grade 3 gastric ulcer bleed due to aspirin use [34]. Clinical trials of ibrutinib have reported grade 3 or higher bleeding in 5% (N = 85; median follow-up: 20.9 months [NCT01105247] [35]) and 1% (N = 195; median follow-up: 9.4 months [NCT01578707] [21]) of patients with relapsed or refractory CLL, and in 4% of patients with treatment naïve CLL (N = 136; median follow-up: 17.4 months [NCT01722487] [36]). The latter two studies [21,36] excluded patients taking warfarin and those with a history of intracranial
hemorrhage. In a trial conducted in patients with CLL or small lymphocytic lymphoma (N = 33) who discontinued ibrutinib (median treatment duration: 10.5 months) owing to ibrutinib-attributable AEs, no major hemorrhage was reported with acalabrutinib treatment at a median follow-up of 9.5 months, including among six patients who previously developed bleeding events while on ibrutinib [22]. Acalabrutinib appears less likely to aggravate or precipitate AEs that lead to ibrutinib discontinuation [22,23].

Headache has been more frequent in acalabrutinib CLL trials (42–43%) [33,34] than in ibrutinib CLL trials (14–18%) [21,35]. All cases of headache reported for acalabrutinib have been grade 1 or 2, have occurred early in treatment and have generally resolved over time, and have not caused any patients to discontinue. Conversely, diarrhea and fatigue have been more common in ibrutinib CLL trials (42–49% and 28–32%, respectively [21,35,36]) than in acalabrutinib CLL trials (35–39% and <15–21%, respectively [33,34]). However, acalabrutinib and ibrutinib have not been directly compared in any head-to-head clinical trials. Such data are necessary to eliminate variations in study design between acalabrutinib and ibrutinib trials that may impact on observed differences in the rates of specific AEs.

In October 2017, the Food and Drug Administration (FDA) approved acalabrutinib for use as a single agent in patients with relapsed or refractory MCL, based on the positive results of a phase 2 study (NCT02213926: Table 1). In this trial, the overall response rate (ORR) for acalabrutinib 100 mg given twice daily to patients with MCL (N = 124) was 81% (complete response in 40%) at a median follow-up of 15.2 months (median duration of response, progression-free survival and overall survival were not reached) [37]. The ORR for ibrutinib 560 mg once daily in the pivotal trial that led to its approval in patients with relapsed or refractory MCL (N = 111) was 68% (complete response in 27%) at a median follow-up of 15.3 months (NCT01236391) [18], although patients in this trial population were more heavily pre-treated and a lower proportion (14%) had low-risk simplified Mantle Cell Lymphoma International Prognostic Index scores than in the acalabrutinib MCL trial (39%) [37].

The most common (≥20%) AEs in the acalabrutinib MCL trial were headache (38%), diarrhea (31%), fatigue (27%) and myalgia (21%) [37]. There were no cases of atrial
fibrillation and only one serious (grade 3) bleeding event (gastrointestinal [GI]
hemorrhage in one patient with a history of a GI ulcer) [37]. In the ibrutinib MCL
trial, the most common (≥ 20%) AEs were diarrhea (50%), fatigue (41%), nausea
(31%), peripheral edema (28%), dyspnea (27%), constipation (25%), upper-
respiratory tract infection (23%) and decreased appetite (21%) [18]. Serious AEs of
atrial fibrillation occurred in five patients (5%) and grade 3 bleeding events also
occurred in five (5%) patients [18].

Acalabrutinib is also being investigated in combination with BR in patients with
untreated MCL (NCT02717624 [phase 1] and NCT02972840 [phase 3]; Table 1), and
in more ‘experimental’ combinations with the phosphoinositide 3-kinase inhibitor
ACP-319 (NCT02328014 [phase 1/2]) and the immune ‘checkpoint’ inhibitor
pembrolizumab (NCT02362035).

3.2. Zanubrutinib (BGB-3111)
Zanubrutinib is an irreversible BTK inhibitor [38,39]. The binding site for this
molecule has not (to our knowledge) been made publicly available. Zanubrutinib
inhibits BTK activity at unspecified nanomolar concentrations in biochemical assays
and inhibits BCR-induced responses (BTK auto-phosphorylation and downstream
PLCγ2 signalling) in several MCL and diffuse large B-cell lymphoma cell lines [40].
Zanubrutinib also has anti-proliferative effects and induces apoptosis in MCL cell
lines, and has similar anti-tumor activity to ibrutinib in a subcutaneous MCL
xenograft mouse model, but at a much lower dosage (2.5 mg/kg twice daily) versus
ibrutinib (50 mg/kg once daily) [40,41].

In a phase 1 study in patients with relapsed or refractory B-cell malignancies,
bioavailability of zanubrutinib 80 mg once daily was similar to that for ibrutinib
560 mg once daily [38]. In addition, a mean 24-hour BTK occupancy of 98.6% was
reported with zanubrutinib 40 mg once daily, compared with greater than 90%
occupancy reported for acalabrutinib 200 mg once daily [42], which was itself
reported as having better target coverage than ibrutinib 420 mg once daily. Of six
patients in the phase 1 study who have MCL, four have had an objective response
(one complete response) after a median follow-up of 227 days [38].
Zanubrutinib is reported as having greater selectivity than ibrutinib for BTK versus EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, BLK and TEC, although specific values were not able to be identified from the literature [38,40]. No drug-related serious AEs or AEs leading to discontinuation have been observed in the phase 1 trial (N=25) of zanubrutinib in patients with relapsed or refractory B-cell malignancies, and no cases of grade 3 or 4 bleeding or of atrial fibrillation (including in four patients with a history of atrial fibrillation) have been reported [38].

Taken together, the above data indicate that zanubrutinib is a potent inhibitor of BTK, with potentially better selectivity, bioavailability and target coverage than ibrutinib. There is one ongoing phase 2 trial of zanubrutinib in patients with relapsed or refractory MCL (NCT03206970; Table 1), but no data are yet available. Although not the focus of the clinical trial searches, it is worth noting that a phase 3 trial comparing zanubrutinib to ibrutinib in patients with Waldenstrom Macroglobulinemia is ongoing (NCT03053440), and should provide useful information regarding the relative toxicity of these two drugs.

3.3. M7583

M7583 is an irreversible inhibitor of BTK. Where this molecule binds to BTK is not clearly described in the literature. Nevertheless, it has high potency, with an IC$_{50}$ of 1.48 nM against purified BTK [43]. M7583 was found to inhibit six (2.2%) of a panel of 270 kinases by more than 50% (ZAP-70, BLK, BMX, TXK, ITK and SKG) at a concentration of 1μM [43], which is comparable to the level of enhanced selectivity exhibited for acalabrutinib versus ibrutinib (inhibition $\geq 65\%$ of 1.5% vs 8.9 of 395 kinases, respectively, at a concentration of 1μM) [27].

M7583 is reported as having relatively low bioavailability of 16%, a short half-life of 45 minutes, and a high (but unspecified) degree of BTK occupancy after dosing in mice, and is currently being investigated in patients with relapsed or refractory B-cell malignancies in a phase 1/2 trial (NCT02825836; Table 1). At the time of reporting, preliminary data from three subjects (one with MCL) enrolled in this trial showed that all had an objective response, or stable disease and a relevant clinical benefit [44].
3.4. SNS-062

SNS-062 is a non-covalent (reversible) BTK inhibitor. The IC$_{50}$ value for SNS-062 against purified BTK is 2.9 nM [45], and this molecule has been shown to inhibit BTK auto-phosphorylation in human whole blood and in mice [45]. In biochemical assays, SNS-062 exhibited binding to eight kinases at a concentration of less than 25 nM, including BTK (0.3 nM) and the TEC kinase family member, ITK (2.2 nM) [45]. SNS-062 has been shown to decrease B-cell activation markers, viability and stromal cell protection in primary CLL cells [46]. Unlike ibrutinib and acalabrutinib, SNS-062 maintains its potent inhibitory activity against both wild-type BTK and cysteine 481 to serine (C481S)-mutated BTK [45,46].

SNS-062 is reported as having good oral bioavailability and tolerability in rats and dogs, with higher continuous drug levels and exposures than ibrutinib [45]. AEs reported in a phase 1 trial of SNS-062 conducted in healthy volunteers included headache in 5 patients (25%) and nausea, bronchitis, fatigue, orthostatic hypotension, and supraventricular tachycardia in one patient (4%) each [47]. There is one ongoing phase 1/2 clinical trial for SNS-062 in patients with B-lymphoid malignancies (NCT03037645; Table 1). No data are yet available for this trial.

3.5. ARQ-531

ARQ-531 is a reversible inhibitor of BTK and has an IC$_{50}$ value of 0.85 nM [48]. Treatment with ARQ-531 inhibits BCR-induced responses (BTK, AKT and ERK phosphorylation) in primary CLL cells [49]. However, this molecule demonstrates off-target activity against a number of other kinases, including the majority of SRC and TEC family kinases [49]. ARQ-531 exhibits better activity than ibrutinib in terms of reducing primary CLL cell viability and increasing survival times in a TCL1 mouse model of leukemia [49]. In addition, ARQ-531 has similar IC$_{50}$ values against both wild-type and C481S-mutated BTK [49]. Treatment with ARQ-531 also reduces the viability of primary CLL cells from patients with C481S-mutated BTK [49], and has anti-proliferative activity against ibrutinib-resistant SUDHL-4 cells in tissue culture and a xenograft mouse model [48].

In a single oral dose study conducted in monkeys, the bioavailability of 10 mg/kg ARQ-531 was 72.4% [49]. This molecule is being investigated in a phase 1 trial in
patients with hematological malignancies (NCT03162536; Table 1). No published data for this clinical trial were identified from our literature searches.

3.6. ONO/GS-4059
Although not mentioned in relation to MCL in ClinicalTrials.gov (and thus not reviewed in detail here), the irreversible BTK inhibitor ONO/GS-4059 should also be mentioned. This molecule had significant activity in patients with relapsed/refractory B-cell malignancies in a phase 1 trial, including in a sub-set of 12 patients with MCL, of whom 11 responded to treatment (median treatment duration: 40 weeks) [50]. Further details of this molecule, which also has greater selectivity compared with ibrutinib, are well summarized in the recent review by Wu and colleagues [26].

4. BTK inhibitor pipeline in the context of MCL guidelines
Figure 1 shows the clinical development status of ibrutinib and new and emerging BTK inhibitors in MCL, in the context of National Comprehensive Cancer Network (NCCN) treatment guidelines [51], which are broadly similar to European guidelines with regard to the use of BTK inhibitors [52]. So far, acalabrutinib is the only new BTK inhibitor to be approved in the USA for MCL. Like ibrutinib, this is in patients who have received at least one prior therapy. All other new and emerging BTK inhibitors are being investigated exclusively in this setting. However, most ongoing clinical trials for acalabrutinib and ibrutinib are exploring experimental combinations (in less-aggressive induction and second-line treatment settings) with drugs not approved in MCL, for which data presumably support some synergy with BTK inhibitors, such as B-cell lymphoma 2 (BCL-2) inhibitors [53], programmed cell death protein 1 (PD-1 [checkpoint]) inhibitors [54] and phosphoinositide 3-kinase (PI3K) inhibitors [55-57]. Only ibrutinib is being investigated in patients with MCL in the aggressive induction setting and as a possible third-line treatment following bortezomib failure or relapse following donor stem cell transplant.

5. Conclusion
New and emerging BTK inhibitors have the potential to further optimize the treatment of patients with this promising class of molecules. Placement of these drugs among MCL treatment guidelines is likely to evolve substantially over the coming years, as
safety and efficacy data from a number of ongoing trials exploring their potential synergy with other drugs, particularly targeted therapies, become available.

6. Expert commentary

The available evidence indicates that covalent, irreversible BTK inhibitors being investigated in patients with MCL (acalabrutinib, BGB-311 and M7583) may have similar potency to ibrutinib, but with reduced off-target activity that could translate into improved safety and tolerability. Favorable clinical data for acalabrutinib raise the possibility that efficacy may also be enhanced, possibly as a result of more complete and continuous inhibition of BTK due to its pharmacokinetic and pharmacodynamic properties, although no head-to-head data are available and therefore differences in the trial populations used may be a factor. The potential for improved safety and tolerability seems less likely to apply to non-covalent, reversible BTK inhibitors being investigated in MCL (SNS-062 and ARQ-531), because these molecules appear to have significant off-target activity against kinases that may be responsible for AEs associated with ibrutinib, including bleeding and atrial fibrillation [58-61]. Where the strengths of these molecules may lie is in their activity against C481S-mutated BTK, an established mechanism of secondary (acquired) ibrutinib resistance in MCL, although alternative mechanisms unrelated to the BTK pathway (e.g. downstream PIK3-AKT pathway activation) may provide a greater contribution to primary ibrutinib resistance in these patients [62]. The relative clinical importance of different ibrutinib resistance mutations in MCL remains an active area of investigation. Other advantages may well exist for these molecules that cannot be easily deduced from the currently available literature. Indeed, most of the available literature on new and emerging BTK inhibitors pertains to acalabrutinib.

In any of the MCL treatment settings being investigated for ibrutinib, a BTK inhibitor with similar (or better) efficacy but an improved safety and tolerability profile would represent an attractive alternative, providing (at the very least) an avenue to continue BTK inhibitor therapy in patients who would otherwise discontinue. AEs associated with ibrutinib are a major impediment to achieving the best possible outcomes with this breakthrough class of molecules. This is particularly relevant to MCL, where the median age at onset is 68 years, meaning that the majority of patients will require less aggressive induction therapy. Both ibrutinib and acalabrutinib are being investigated
Finally, it should be noted that, while data from single arm trials do indicate a more favourable AE profile for acalabrutinib versus ibrutinib, no head-to-head data are yet available. Such data are important for addressing the potential effects of study design variation on observed safety profiles, such as exclusion criteria that could influence rates of bleeding and atrial fibrillation with these drugs. To this end, an ongoing phase 3 head-to-head study of ibrutinib and acalabrutinib in patients with relapsed or refractory CLL (NCT02477696) will be particularly useful in cementing differences in the safety profiles of these drugs that have been hinted at in trials conducted to date.

7. Five-year view

It is expected that several key trials in MCL will read out in the next year or two. This will include the use of BTK inhibition with BR versus BR alone (NCT01776840). If positive, then BTK inhibition will be included in the upfront treatment of patients with MCL. The next logical question is whether the chemotherapy (bendamustine) component is required, or whether the addition of a CD20 antibody (rituximab) is sufficient. Early data from the MD Anderson Cancer Centre show a response rate of 100% has been achieved when ibrutinib plus rituximab is used upfront. A UK trial comparing rituximab-CHEMO (Bendamustine OR CHOP [cyclophosphamide, doxorubicin, vincristine and prednisone]) with rituximab-ibrutinib as front-line therapy for elderly patients is ongoing. If positive, chemotherapy-free treatment will become the new standard of care for elderly patients. In the relapse setting, BTK inhibition has been combined with BCL-2 inhibition in a phase 2 trial (NCT02471391), and a randomized phase 3 trial has started as well (NCT03112174). If positive, the BTK inhibitor plus BCL-2 inhibitor combination will be a new standard in relapsed or refractory MCL. It could then also be possible to have an upfront chemotherapy free regimen in elderly patients that includes BTK inhibition plus BCL-2 inhibition plus anti-CD20 monoclonal antibody therapy. While no such trials are currently underway, one might expect their initiation in the next few years. The field is truly exciting with novel agents having significant activity.
8. Key issues

- Outcomes for patients with mantle cell lymphoma (MCL) have improved with the introduction of upfront aggressive and target therapies, but the disease remains incurable with the possible exception of allograft.
- The clinical benefits of ibrutinib, the first Bruton tyrosine kinase (BTK) inhibitor approved in MCL (as second-line treatment), are becoming clear, but adverse events due to off-target effects warrant refinement of this drug class.
- The available literature suggests that new (acalabrutinib) and emerging (zanubrutinib [BGB-3111], M7583) covalent, irreversible inhibitors under investigation in MCL have similar potency to ibrutinib, but with fewer off-target effects.
- Non-covalent, reversible BTK inhibitors under investigation in MCL (SNS-062, ARQ-531) may not be as selective as covalent, irreversible inhibitors, but could have activity against some ibrutinib-resistant B-cell malignancies.
- Trials of acalabrutinib, which has now been approved in the USA as second-line treatment for MCL, suggest that both safety and efficacy could be enhanced versus ibrutinib, although no head-to-head data are yet available.
- Placement of BTK inhibitors in MCL treatment guidelines will likely evolve substantially over the coming years, as the results of trials exploring earlier use of these drugs (e.g. as less-aggressive induction therapy), and their potential synergy with other targeted therapies, become available.

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Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.
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Papers of special note have been highlighted as:

* of interest
** of considerable interest


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This paper summarizes preclinical and early phase clinical evidence of greater potency and selectivity for acalabrutinib versus ibrutinib, which led to the investigation of this molecule in phase 2 clinical trials in patients with B-cell malignancies.


53. Deng J, Isik E, Fernandes SM, et al. Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia. Leukemia. 2017; 31(10):2075–2084. This study demonstrated synergy between Bruton tyrosine kinase inhibitors and BCL-2 inhibitors in terms of their ability to kill primary CLL cells. This promising combination is now being tested in a phase 3 clinical trial (NCT03112174).


Table 1. Details of ongoing clinical trials of new and emerging Bruton tyrosine kinase inhibitors in patients with mantle cell lymphoma (identified from ClinicalTrials.gov search conducted on 15 August 2017).

<table>
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<tr>
<th>Study ID</th>
<th>Intervention</th>
<th>Condition</th>
<th>Phase</th>
<th>Primary endpoint(s)</th>
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<th>Completion</th>
<th>Approvals</th>
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<td>ORR (at least 1 year)</td>
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<td>Feb 2017</td>
<td>FDA (Oct 2017)</td>
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<td>Acalabrutinib + ACP-319</td>
<td>NHL, MM and B-ALL(^b)</td>
<td>1/2</td>
<td>AEs (up to 1 year)</td>
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<td>Aug 2017</td>
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<td>CT-1530</td>
<td>R/R BCNLH, CLL, MCL, WM, MZL, DFCL and DLBCL</td>
<td>1/2</td>
<td>DLTs (28 days) MTD and/or RP2D</td>
<td>200(^c)</td>
<td>Sep 2018</td>
<td>None</td>
</tr>
<tr>
<td>NCT03037645</td>
<td>SNS-062</td>
<td>R/R CLL, LL, MCL, SLL and WM</td>
<td>1/2</td>
<td>MTD and/or RP2D (up to 21 months) ORR (up to 24 months)</td>
<td>124(^c)</td>
<td>Sep 2018</td>
<td>None</td>
</tr>
<tr>
<td>NCT03206970</td>
<td>BGB-3111</td>
<td>R/R MCL</td>
<td>2</td>
<td>ORR (up to 3 years)</td>
<td>80(^c)</td>
<td>Nov 2018</td>
<td>None</td>
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<tr>
<td>NCT03162536</td>
<td>ARQ-531</td>
<td>R/R BCL, DLBCL, SLL, CLL, MCL, WM</td>
<td>1</td>
<td>AEs (up to 28 weeks) RP2D (up to 24 weeks)</td>
<td>120(^c)</td>
<td>Dec 2018</td>
<td>None</td>
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<tr>
<td>NCT02825836</td>
<td>M7583</td>
<td>R/R BCM, MCL and DLBCL</td>
<td>1/2</td>
<td>DLTs (up to 28 days) BOR (up to 6 months)</td>
<td>60(^c)</td>
<td>Oct 2019</td>
<td>None</td>
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<tr>
<td>NCT02717624</td>
<td>Acalabrutinib + BR</td>
<td>Untreated and R/R MCL</td>
<td>1b</td>
<td>TEAEs (timeframe unclear)</td>
<td>48(^c)</td>
<td>Feb 2021</td>
<td>None</td>
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<tr>
<td>NCT02362035</td>
<td>Acalabrutinib + Pembrolizumab</td>
<td>NHL, MM, HL, CLL, RS, WM(^b)</td>
<td>1b/2</td>
<td>TEAEs (2 years)</td>
<td>159</td>
<td>Apr 2021</td>
<td>None</td>
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<tr>
<td>NCT02972840</td>
<td>Acalabrutinib + BR vs placebo + BR</td>
<td>Untreated MCL</td>
<td>3</td>
<td>PFS (48 months)</td>
<td>546(^c)</td>
<td>Oct 2022</td>
<td>None</td>
</tr>
</tbody>
</table>

AE, adverse event; B-ALL, B-cell acute lymphocytic leukemia; BCL, B-cell lymphoma; BCM, B-cell malignancies; BCNLH, B-cell non-Hodgkin lymphoma; BOR, best overall response; BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; DFCL, diffuse follicle center lymphoma; DLBCL, diffuse large B-cell lymphoma; DLTs, dose-limiting toxicities; HL, Hodgkin lymphoma; LL, lymphoplasmacytoid lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NHE, non-Hodgkin lymphoma; ORR, overall response rate; PFS, progression-free survival; RP2D, recommended phase 2 dose; R/R, relapsed or refractory; RS, Richter’s syndrome; SLL, small lymphocytic leukemia; TEAE, treatment-emergent adverse event; WM, Waldenstrom macroglobulinemia.

\(^a\) Estimated primary completion date.
\(^b\) MCL not specifically mention among listed conditions, but was included among keywords submitted for the study.
\(^c\) Estimated enrolment number.
BR, bendamustine + rituximab; DSCT, donor stem cell transplant; L/R, lenalidomide/rituximab; NCCN, National Comprehensive Cancer Network; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone; R-DHAP, rituximab + dexamethasone + cytarabine + cisplatin; R-DHAOx, rituximab + dexamethasone + cytarabine + oxaliplatin

<table>
<thead>
<tr>
<th>BR, bendamustine + rituximab</th>
<th>DSCT, donor stem cell transplant</th>
<th>L/R, lenalidomide/rituximab</th>
<th>NCCN, National Comprehensive Cancer Network</th>
<th>R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone</th>
<th>R-DHAP, rituximab + dexamethasone + cytarabine + cisplatin</th>
<th>R-DHAOx, rituximab + dexamethasone + cytarabine + oxaliplatin</th>
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</thead>
<tbody>
<tr>
<td>Includes treated and untreated patients.</td>
<td>MCL not specifically mention among listed conditions, but was included among keywords submitted for the study.</td>
<td>Malignancies other than MCL also included in the trial population.</td>
<td></td>
<td></td>
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</table>

**Figure 1.** Trials of Bruton tyrosine kinase (BTK) inhibitors in the context of National Comprehensive Cancer Network (NCCN) guidelines for the treatment of mantle cell lymphoma (MCL). New and emerging BTK inhibitors are highlighted in bold black text. Red text indicates drugs that are being tested in combination with BTK inhibitors that are not currently recommended anywhere in NCCN treatment guidelines for MCL. Molecules within blue (rather than green) arrows are BTK inhibitors where there is reasonable evidence of enhanced BTK selectivity that could translate into improved safety and tolerability over ibrutinib in an equivalent indication under investigation. Clinical trials of new and emerging BTK inhibitors were identified from the results of the initial ClinicalTrials.gov search (presented in Table 1). Clinical trials of ibrutinib were identified using a supplementary search conducted on 27 October 2017 for trials including terms for ibrutinib AND MCL. Unless otherwise indicated, trials are in patients with MCL only.