REVIEW ARTICLE

blood advances

BTK inhibitors in CLL: second-generation drugs and beyond

Constantine Tam[1,2] and Philip A. Thompson[3,4]

[1]Department of Haematology, Alfred Hospital, Melbourne, VIC, Australia; [2]Haematology, Monash University, Melbourne, VIC, Australia; [3]Clinical Haematology, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, VIC, Australia; and [4]The Sir Peter MacCallum Department of Clinical Oncology, The University of Melbourne, Melbourne, VIC, Australia

BTK inhibitors (BTKis) are established standards of care in multiple B-cell malignancies including chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom macroglobulinemia. The first-generation BTKi ibrutinib demonstrated superiority over standard chemoimmunotherapy regimens in multiple randomized trials but is limited by cardiovascular side effects such as atrial fibrillation and hypertension. Second-generation BTKis have improved selectivity and demonstrate reduced rates of cardiovascular complications in 3 head-to-head ibrutinib studies. The emergence of BTK C481S mutation has led to the development of noncovalent, "reversible" BTKis, such as pirtobrutinib, which are agnostic to the C481S mutation. However, these inhibitors are associated with resistant mutations outside the C481 hot spot. These variant non-C481 mutations are of great clinical interest because some are shared among pirtobrutinib, zanubrutinib, and acalabrutinib, with potential implications for cross resistance and treatment sequencing. Finally, BTK protein degraders with in vitro activity against C481 and non-C481 mutations are currently in clinical development. Here, we review the evolution of therapeutic BTK-targeting and discuss future directions for clinical research.

BTK: a "perfect" target?

In 1952, Colonel Ogden Bruton of Walter Reed Hospital described a congenital disease in babies born with severe immunodeficiency due to the absence of B-cell maturation and agammaglobulinemia.[1] This was eventually identified to be due to mutations in the *BTK* gene encoding a critical protein in the B-cell receptor pathway.[2] The disease phenotype was entirely restricted to the B-cell lineage and affected children grew up and survived into midadulthood with no other clinically manifested organ dysfunctions.[3]

Fast forward to the present day, BTK inhibitors (BTKis) are the standard of care in multiple B-cell malignancies including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenstrom macroglobulinemia (WM), and marginal zone lymphoma[4] and have recently been approved for use in Europe in relapsed follicular lymphoma, in combination with obinutuzumab, based on the results of the ROSEWOOD study.[5] The widespread use of BTKi in the clinic led to the emergence of new problems including the occurrence of cardiovascular[6] and bleeding side effects[7] and the development of resistance mutations.[8] New classes of "second-generation" and "reversible" BTKis were developed in response.[9] In this review, we discuss the history and recent updates in the ongoing cat-and-mouse race between clinician-scientists and the continuously mutating B-CLL cell.

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First-generation BTKi: ibrutinib

Many younger hematologists did not experience the dismal treatment landscape of chemotherapy-refractory CLL before BTKi. Before ibrutinib, our most promising "novel agents," such as alemtuzumab, achieved short-term remissions in <35% of patients,[10] with substantial side effects including immunosuppression and myelosuppression in patients with little remaining marrow reserve. The median survival of patients with chemotherapy- and alemtuzumab-refractory CLL was 9 months.[11]

In that context, the outcomes of ibrutinib (PCI-32765) in early clinical trials can only be described as miraculous. Most patients, including those who were refractory to all previous therapies, responded rapidly.[12] Patients with severe cytopenia improved their blood counts, and infections were uncommon. Poor prognostic markers, including unmutated IgHV and del(11q), lost their clinical relevance,[13] and improvement in outcomes for patients with the highest risk with *TP53* deletion were particularly notable, with a median progression-free survival (PFS) of 26 months in this group in the phase 1b/2 PCYC 1102 study[14] and 41 months in a slightly less heavily pretreated population in the randomized RESONATE trial.[15]

Given the remarkable efficacy in difficult-to-treat patients with relapsed/refractory (R/R) disease, including those with high-risk genomics, as well as its favorable toxicity profile, ibrutinib was rapidly evaluated in the first-line setting. There, it demonstrated superior PFS and overall survival (OS) in older patients in the RESONATE-2 trial (compared with chlorambucil)[16] and in younger patients in the E1912 study (compared with FCR).[17] Furthermore, notable were the impressive PFS rates of ~60% at 6 years in patients with *TP53* aberrations treated with first-line ibrutinib.[18,19]

Amid the excitement of this new therapy, interesting observations emerged from the clinic. Although ibrutinib was largely free of infectious and marrow toxicities, patients developed bleeding[20] and atrial fibrillation.[21] These were side effects not expected from BTK blockade, because patients with congenital BTK deficiency do not have bleeding or cardiac phenotypes.[3] With more widespread use of ibrutinib, late hypertension[22] and rare, fatal ventricular arrhythmias (VAs)[23,24] emerged as new important side effects. Investigations into platelet and cardiovascular toxicities identified BTK as being crucial in platelet and cardiac signaling.[25] Although these toxicities are technically "on-target" in nature, they are seen with drug therapy and not with congenital BTK deficiency for 1 key reason: congenital deficiency affects BTK only, and proteins closely related to BTK (such as the TEC family of kinases)[26] are able to provide "backup" signaling in organs outside of the B-cell compartment. In contrast, drug therapy is not as specific as gene knockout, and the inhibition of BTK and structurally related kinases resulted in disabling of signaling pathways outside the B-cell compartment including platelets and cardiac myocytes.[25]

The solution to this problem is to develop cleaner, more specific BTKi with less off-target kinase inhibition.

Second-generation BTKis

The term "second-generation BTKis" encompasses multiple drugs all of which have 1 factor in common: higher specificity for BTK with reduced off-target kinase inhibition than ibrutinib. This class includes acalabrutinib (ACP-196), zanubrutinib (BGB-3111), tirabrutinib (ONO-4059), and orelabrutinib. The 2 exemplars of this class are acalabrutinib and zanubrutinib, with both having been compared with ibrutinib in head-to-head trials (Table 1).

Acalabrutinib

The phase 1 results of acalabrutinib were published in 2016.[27] Acalabrutinib was 3× more selective for TEC, 10× more selective for BMX, and >100× more selective for ERBB2, EGFR, ITK, and JAK3 than ibrutinib.[28] Acalabrutinib has a short half-life, and twice-daily dosing was required to sustain blood BTK inhibition of >95%.[29]

The initial trials with acalabrutinib reported a favorable adverse event (AE) profile compared with the historical experience with ibrutinib. This impression was confirmed in the head-to-head ELEVATE-RR phase 3 comparison of acalabrutinib vs ibrutinib[30] in patients with high-risk R/R CLL, in which reduced rates of AF, bleeding, and hypertension were seen in the acalabrutinib arm. ELEVATE-RR was a noninferiority study, and the PFS of the ibrutinib and acalabrutinib arms were equal. Acalabrutinib was associated with 2 problems not seen with ibrutinib: (1) a headache that is common in patients during the first weeks of therapy, often responds well to caffeine, and generally improves over time despite continued acalabrutinib therapy;[31] and (2) incompatibility with proton pump inhibitors because of pH-dependent absorption, a problem that is now solved with the new tablet formulation.[32] In the first-line setting, acalabrutinib ± obinutuzumab was compared with chlorambucil + obinutuzumab in the ELEVATE-TN study in older and/or unfit patients. This study demonstrated significant PFS benefit and, in the case of the acalabrutinib + obinutuzumab arm, OS benefit, compared with the chlorambucil + obinutuzumab arm.[33,34] Based on its high efficacy and favorable safety profile, acalabrutinib is licensed for treatment of CLL in any line of therapy and R/R MCL. The ongoing AMPLIFY study (NCT03836261) compares combination therapy with acalabrutinib + venetoclax ± obinutuzumab with FCR in fit patients.

Zanubrutinib

The phase 1 results of zanubrutinib in patients with B-cell malignancies were published in 2019.[35] Zanubrutinib was 2.4× more selective for TEC, 10× more selective for EGFR, and >30× more selective for HER2, ITK, and JAK3 than ibrutinib.[35] At the clinical dose of 160 mg twice-daily, drug exposure to zanubrutinib (as measured by area under the curve) was 8-times higher than that of ibrutinib, and the median BTK occupancy in lymph node biopsies was 100%.[35]

Similar to acalabrutinib, the initial clinical experiences with zanubrutinib reported a favorable AE profile compared with that of ibrutinib.[35] The first head-to-head comparison of zanubrutinib vs ibrutinib was conducted in patients with WM (ASPEN study).[36] Although ASPEN failed to meet its primary end point of superior complete and very good partial response rates in zanubrutinib-treated patients, it was, to our knowledge, the first study in the world to report the AE profile of 2 BTKis head-to-head. In this comparison, zanubrutinib was associated with reduced rates of AF, hypertension, and "nuisance" BTKi side effects such as diarrhea and edema.[36] The rate of neutropenia was increased in the zanubrutinib arm, but no difference in infection rates were noted.

The second head-to-head study comparing zanubrutinib with ibrutinib was the ALPINE study in R/R CLL. ALPINE showed superior overall response rates (ORRs) and PFS in favor of zanubrutinib, with preservation of the superiority in key prognostic groups including those with del(17p). Similar to ASPEN, reduced rates of AF were noted in the zanubrutinib arm. Different from ASPEN, the rate of hypertension was not reduced in ALPINE, and no differences in neutropenia were noted.[37]

Zanubrutinib is now approved as 1L therapy for CLL, based on the SEQUOIA study,[38] which demonstrated superiority relative to bendamustine and rituximab in older and/or unfit patients without del(17p).

Cardiovascular toxicities of second-generation BTKis

In total, 3 head-to-head phase 3 comparisons of ibrutinib vs a second-generation BTKis have been reported. All 3 studies were concordant in showing a reduction in the risk of AF by 2 to 4 times in favor of acalabrutinib or zanubrutinib.[30,36,37] Acalabrutinib was also associated with a significant reduction in the rates of hypertension relative to ibrutinib (acalabrutinib: 9%; ibrutinib: 23%),[30] whereas the rates of hypertension were numerically lower with zanubrutinib in ASPEN (zanubrutinib: 15%; ibrutinib: 26%)[36] and not different in ALPINE (zanubrutinib: 24%; ibrutinib: 23%).[37] The reasons for the differences in hypertension signal reported between acalabrutinib vs zanubrutinib are not known.

Sudden death/VAs are an emerging class-effect of BTKi. The rate of VA is estimated to be 0.6 to 0.8 per 100 person-years for ibrutinib.[24,39] For acalabrutinib and zanubrutinib, the reported VA rates are 0.4[40] and 0.1 per 100 person-years, respectively.[41] These rates are associated with low confidence given their rarity and less experience with the new drugs relative to ibrutinib. More follow-up and surveillance are required.

BTK C481S resistance mutation

Ibrutinib and all second-generation BTKis have relatively short half-lives and achieve continuous BTK inhibition by irreversible (covalent) binding to BTK at the cysteine 481 (C481) residue.[42] Mutations at the BTK C481 site associated with ibrutinib resistance were first reported in 2014.[8,43] Although activating mutations in PLCy (the protein immediately downstream of BTK) were also described, most PLCy mutations occur at low variant allele fractions in patients with concomitant BTK mutations, and isolated PLCy mutations as a cause of BTKi resistance are uncommon.[44]

The canonical C481S mutation accounts for >90% of BTK mutations seen in ibrutinib-treated patients and results in the loss of covalent binding for ibrutinib and all second-generation BTKis. Unlike the variant "loss of function" C481F/Y/W/G/R and L528W mutations that will be discussed later, C481S preserves the kinase activity of the BTK protein. There are more limited data on mutational patterns for acalabrutinib and zanubrutinib. The largest series of acalabrutinib-resistant patients comes from the ELEVATE-RR study. This demonstrated that C481S mutations remain the most common cause of resistance in acalabrutinib-treated patients, but T474I gatekeeper mutations also occur in 29% of patients with acalabrutinib resistance, either alone or in combination with C481S mutations.[45] Similarly, only small data sets exist for zanubrutinib-treated patients, but 1 series showed that L528W kinase-impaired mutations were as frequent as C481S mutations in patients treated with zanubrutinib.[46] Data from ALPINE surprisingly showed an overall lower rate of *BTK* mutations at disease progression, in both the ibrutinib and zanubrutinib arms: in 52 patients (24 treated with zanubrutinib) with paired mutational data before treatment and at progression, only 8 developed *BTK* mutations (5/24 patients treated with zanubrutinib). In the zanubrutinib-treated patients, 3 of 5 patients with *BTK* mutations had non-C481 *BTK* mutations. More data are required to fully understand both the true frequency of non-C481 *BTK* mutations during second-generation BTKi therapy and their impact on response to subsequent therapy.[47]

C481S effectively confers pan-resistance to all available covalent BTKis. The solution to C481S is to develop new BTKis that do not bind to the C481 site.

Reversible, noncovalent BTKis

The somewhat confusingly named "reversible" BTKis differ from the first- and second-generation ones in that they bind BTK reversibly at a site other than C481. The drug that is in most advanced clinical development is pirtobrutinib (LOXO-305). Pirtobrutinib complexes to wild-type and C481S-mutated BTK with equipotent binding affinity and kinase inhibition, and as such, it was predicted to be active in patients carrying the resistant C481S mutation.[48] Although the binding of pirtobrutinib to BTK is reversible in nature, the long half-life of 20 hours meant that the clinical dose of 200 mg once daily was sufficient in reaching a trough plasma concentration resulting in 96% BTK inhibition throughout the dosing interval.[48]

Indeed, in the phase 1 study of pirtobrutinib in patients with B-cell malignancies, the drug demonstrated high activity in patients with CLL, WM, and MCL. Updated data from the cBTKi–exposed CLL cohort of the BRUIN study at American Society of Hematology (ASH) 2023 showed a PFS of 19.4 months, (23 months in BCL2 inhibitor–naïve and 15.9 months in BCL2 inhibitor–exposed patients).[49] As expected from the preclinical data, there was no apparent disadvantage seen in those patients known to carry the C481S mutation.[50] Fascinatingly, the drug also demonstrated high response rates in patients with CLL who did not have *BTK* mutations and in even those with *PLCG2* mutations, demonstrating that, in those patients, BTK remained a relevant therapeutic target. The precise molecular mechanisms underpinning this phenomenon are currently unclear. An additional advantage of pirtobrutinib is its very high specificity for BTK, with very little off-target kinase activity. Indeed, the AE profile of pirtobrutinib from the phase 1 study was favorable, similar (or perhaps superior) to the AE profiles seen with second-generation cBTKis.[51]

Several other reversible BTKis are in clinical development. As a class, these drugs share the "C481S agnostic" characteristic of pirtobrutinib in the laboratory, and clinical responses are reported in patients carrying the C481S mutation. Different from pirtobrutinib, these other reversible BTKis tend to be less specific for BTK, with more off-target kinase affinity than pirtobrutinib. For example, nemtabrutinib (ARQ-531 and MK-1026) has TEC and BMX off-kinase activity, whereas vecabrutinib (SNS-062) has some cross interaction with both ITK and TEC.

Until recently, inhibitors with high specificity, such as the second-generation BTKis and pirtobrutinib, were seen to be desirable in the clinic due to the potential for reduced AEs. However, more

recent reports have shown that variant (non-C481S) BTK mutations may be more common in patients treated with highly specific drugs such as acalabrutinib, zanubrutinib, and pirtobrutinib. These mutations include (1) "kinase-dead" mutations at C481 (C481F, C481Y, C481W, C481G, and C481R); (2) a second kinase-dead mutation at L528W; (3) "gatekeeper" mutations at T474 (T474I or T474L); and (4) other less common mutations such as A428D, M477I, and V416L.[52] Fascinatingly, in the setting of "kinase-dead" mutations, in which BTK kinase activity is abrogated, as demonstrated by autophosphorylation at the Y223 residue, downstream signaling, as evidenced by AKT and ERK phosphorylation, is intact. This suggests an alternative "scaffolding" function of BTK, in which the enzyme facilities recruitment and activation of other signaling molecules, such as LYN, SYK, and HCK to maintain B-cell receptor signaling.[52]

The reason for the emergence of variant BTK mutations with later generation drugs is not known, but in vitro modeling showed that ibrutinib had broad activity against BTK variant mutants, either directly or via off-target inhibition of HCK, which complexes with BTK kinase-dead mutants and restores the signaling capacity of the otherwise apparently inactive mutant.[53] Conversely, pirtobrutinib has little activity against a broad range of BTK variant mutants. Interestingly, other reversible BTKis such as nemtabrutinib and vecabrutinib have some coverage against BTK variant mutants in vitro.[52] In a phase 1 trial, nemtabrutinib has shown clinical activity in heavily pretreated patients with prior cBTKi exposure, with an ORR of 56%.[54] Recruitment to this study and a suite of phase 3 studies comparing nemtabrutinib with standard of care is ongoing. Clinical development of vecabrutinib has not proceeded beyond the phase 1 trial, which demonstrated insufficient activity to justify further development in B-cell malignancies.[55]

An intriguing new molecule, with early results presented at ASH, is LP-168, which binds wild-type BTK covalently and binds noncovalently in the setting of C481S mutation. The molecule is highly selective for BTK and was well tolerated, with no DLTs identified. ORR was 75% at doses of ≥200 mg per day, and 5 of 7 patients with gatekeeper T474I mutation responded.[56]

New directions: BTK degraders

The emergence of multiple BTK mutants under selective pressure gave impetus to the development of a new class of BTK-targeting drugs: BTK protein degraders. These drugs use the ubiquitin-proteasome pathway to ubiquitinate BTK protein in the cell, leading to proteasomal destruction of BTK. Preclinical experiments show broad activity of BTK protein degraders across the spectrum of wild-type and mutant BTKs, including C481S, L528W, T474I, and V416L.[57]

The first clinical results of the BTK degrader class came from a first-in-human study of NX-2127. Preliminary results of this study showed rapid degradation of BTK in B cells of patients on treatment, with reduction in nodal disease in 11 of 14 assessable patients, including those known to carry BTK mutations.[58] Other BTK degraders under clinical investigation include BGB-16673 and UBX-303061. Data presented from the BGB-16673 study at ASH demonstrated a 70% ORR in 10 patients with CLL, with an overall manageable safety profile.[59] If successful, BTK degraders may represent an interesting alternative to kinase inhibition, particularly in those patients who carry multiple BTK mutant clones from prior BTKi exposure.

Perspectives on sequencing in the era of novel BTK mutations

In medicine (and in general life), there is a tendency for clinicians and scientists to be excited about the latest and greatest. When the broad activity of pirtobrutinib in patients with and without BTK C481S mutation was reported, there was great excitement about pirtobrutinib potentially supplanting the first- and second-generation BTKis. We now understand that successful inhibition of C481S mutants may lead to the emergence of variant mutants such as L528W (conferring resistance to zanubrutinib) and T474I (conferring resistance to acalabrutinib). In fact, after a decade of research into new generation BTKis, there may be an enduring place for ibrutinib in the clinic as the agent with the broadest variant mutant coverage.

How do we incorporate all of this knowledge in the clinic? First, how we sequence our drugs in the clinic should be driven by the clinical data from pivotal studies, rather than theoretical concerns about potential for resistance mutations, because knowledge about variant BTK mutations is scarce at present. In this respect, both acalabrutinib and zanubrutinib were proven to be safer than ibrutinib in randomized head-to-head studies, and as such, acalabrutinib and zanubrutinib remain the standard of care; pirtobrutinib and reversible BTKis are clearly active in patients who relapse after covalent BTKi, and their greatest utility is as next-line therapy after covalent BTKi. Second, it is clear that broad sequencing of BTK for mutants is required after every line of BTK-targeting therapy, both in clinical trials and in standard clinical practice, to enable individualized selection of subsequent treatment based on mutant pattern and predicted sensitivity to alternative BTK-targeting strategies. Last, BTKi manufacturers need to evaluate their agent's activity in BTK variant mutants and publish their results. This knowledge will permit the design of the next generation of clinical trials that takes into account the mutational spectrum of the individual patient and matches that spectrum against the most active agent.

Combining BTK inhibition with other agents: potential for limited-duration regimens

There is no denying that BTK inhibition has markedly improved outcomes for all patients with CLL. Nowhere has this been more evident than for patients with *TP53* deletion or mutation who have a median PFS of ~1 year with FCR but who can expect a 6-year PFS of ~60% with ibrutinib.[19,60] However, as we have alluded to above, there are several limitations that mean we do not yet have an "imatinib for CLL." Most notably, real-world data reveal high rates of discontinuation of ibrutinib from AEs, up to 41% at 18 months in some series.[61] Continuous BTKi therapy is required for durable responses in most patients, due to rarity of complete responses and undetectable measurable residual disease (U-MRD); as a result, discontinuation from AEs significantly reduces the potential to achieve long-term PFS. Additionally, especially in high-risk and relapsed CLL, emergence of mutations conferring resistance remains problematic, as outlined above.

Several studies have evaluated combination approaches to deepen remissions and potentially reduce the development of resistance by using agents with nonoverlapping mechanisms of action. At the

Table 1. Comparison of selected BTK-targeting agents

Class	Drug	Binding to BTK	Half-life	Specificity	Toxicity	BTK mutations
First-generation	Ibrutinib	Irreversible at C481	Short	Low	Bleeding, cardiac	C481S
Second-generation	Acalabrutinib	Irreversible at C481	Short	High	Reduced	C481x, T474x
	Zanubrutinib	Irreversible at C481	Short	High	Reduced	C481x, L528W
Reversible	Pirtobrutinib	Reversible	Long	Very high	Reduced	T474, L528W, V416L, A428D, M477I, M437R, kinase-dead C481
	Nemtabrutinib	Reversible	Long	Low	Insufficient data	Not reported
Bifunctional	LP-168	Irreversible at wild-type C481. Reversible in C481S	Long	Very high	Reduced	Not reported
Protein degraders	NX-2127	Degrades BTK	Not reported	Not reported	Insufficient data	Not reported
	BGB-16673	Degrades BTK	Long	Not reported	Insufficient data	Not reported

most straightforward level, obinutuzumab has been added in the first-line setting to ibrutinib in the ILLUMINATE trial[62] and to acalabrutinib in the ELEVATE-TN study.[34,63] The 4 year follow-up of this study[63] demonstrated an 87% PFS in the A + O arm vs 78% in the acalabrutinib monotherapy arm ($P = .0296$). This study used continuous BTK inhibition until progression in the A + O arm and was thus not designed to alter the treat-to-progression paradigm of BTKi monotherapy.

Contrary to this study, numerous studies in first-line and relapsed CLL have evaluated various time-limited combinations of BTKis with the BCL2 inhibitor venetoclax, either with or without obinutuzumab (Table 2). Both fixed-duration and MRD–adapted treatment-duration approaches have been tested. Relative to fixed-duration therapy of 1 year with ibrutinib + venetoclax (I + V), there does appear to be deepening of remissions in a proportion of patients during second year of therapy.[64-67] Studies of I + V have demonstrated that this approach is generally well tolerated, with high rates of achievement of U-MRD and durable off-treatment remissions in a high proportion of patients (with albeit a relatively short duration of follow-up for most of these trials). I + V has been approved by the European Medicines Agency based on the GLOW trial, which randomized older and unfit patients to I + V vs chlorambucil and obinutuzumab (O + Clb).[68] At the latest follow-up, this study has demonstrated a survival advantage for I + V vs O + Clb; however, the regimen has not been approved for use by the US Food and Drug Administration for use in the United States, due, in part, to a higher rate of early deaths (including 4 cardiac/sudden deaths) in the I + V arm. Of note, I + V was associated with greater tolerability and lower risk of cardiac AEs in the CAPTIVATE trial (which enrolled younger, fitter patients) than in GLOW, a finding that has been recapitulated right across the BTKi development programs.[66,69] The 1-year fixed-duration arm of CAPTIVATE also showed a higher rate of U-MRD4 than GLOW.[69] A somewhat surprising finding from GLOW (also replicated in other I + V studies) was that patients with mutated IgHV have lower rates of achievement of U-MRD4 than patients with unmutated IgHV.[68] However, despite this, they have highly favorable PFS, with >90% remaining progression-free at 3.5 years of follow-up, with remarkably stable MRD levels on serial analysis.[70] At the current follow-up, no statistically significant difference in PFS has been seen between patients who have MRD positivity vs U-MRD4. Longer follow-up is clearly required, but this does raise the prospect that U-MRD4 may not be absolutely required for prolonged treatment-free remission after I + V, especially in patients with mutated IgHV, who have slower clonal growth rates.[71,72]

Much debate is ongoing in the field about the role of I + V in the first-line setting and which patients should be considered for this treatment in preference to V + O or continuous BTKi therapy. Many CLL-focused clinicians feel instinctively uncomfortable with the idea of combining the 2 best drug classes (BTKi and venetoclax) first line, expressing concern about the availability of effective salvage therapy at progression. In this regard, more data are required, but it is notable that very few patients develop canonical resistance mutations to BTKi or venetoclax during/after time-limited I + V combination therapy,[73,83] in contrast to the use of the single-agent treat-to-progression approach. Additionally, the early, emerging data from the fixed-duration cohort of CAPTIVATE have demonstrated near-universal response to retreatment with ibrutinib monotherapy after progression (15/17 responses; only 1 patient with progressive disease).[84] There are very limited data on re-treating with a BTKi + BCL2 inhibitor doublet. Whether combination approaches are superior to sequential monotherapy is a challenging question and one in which the traditional end point of PFS is inadequate to answer. As an example, when comparing continuous BTKi therapy with BTKi + BCL2i (±CD20 antibody) given for a fixed duration, the continuous BTKi may show similar or even superior PFS, as demonstrated by the early results from the Alliance A041702 trial. However, by definition, a patient progressing on continuous BTKi will have resistant disease, whereas most patients progressing after fixed-duration BTKi + BCL2i remain sensitive to retreatment with BTKi[83] (with very limited data available on venetoclax retreatment in this setting). An end point such as time to treatment failure may better answer this question, but we acknowledge the challenges in the implementation of such a design, particularly the time frames required to obtain an answer in a population of patients with generally excellent outcomes. The fully accrued ECOG9161 trial (NCT03701282), which enrolled younger patients, and the fully accrued German CLL study group CLL17 trial (NCT 04608318), which enrolled patients regardless of age, test a similar concept to A041702 (fixed-duration combination therapies vs BTKi monotherapy). It will be of great interest to follow long-term results of these studies, especially PFS after second-line therapy. The jury remains out on whether fixed-duration treatment of response-adapted treatment is optimal when combining BTKi + BCL2i. Two phase 3 studies of note, evaluating alternative approaches, are the MAJIC study, comparing venetoclax + obinutuzumab with acalabrutinib + venetoclax, with both arms allowing for MRD–adapted treatment duration, and the UK MRC FLAIR trial. The latter study recently reported a PFS and OS benefit for MRD-adapted I + V compared with FCR and an overall highly favorable PFS for the I + V arm.[85]

Table 2. Selected studies of BTKi + BCL2i ± CD20 antibody

Study	Regimen	Population	CR/CRi	U-MRD4	PFS/OS
1L "Doublets"					
M.D. Anderson phase 2,[64,65] n = 80	I, 3 cycles; then I + V, 24 cycles; MRD–adapted I maintenance; then third year of I + V	TN; ≥65 y or high-risk genomics*	78 (best)	75 (BM-best)	93/96 (3 y)
CAPTIVATE FD[73] phase 2, n = 159	I, 3 cycles; then I + V, 12 cycles; FD	TN; 18-70 y	55.9	77 (PB)/60 (BM)	95/96 (2 y)
CAPTIVATE MRD[66] phase 2, n = 164	I, 3 cycles; then I + V, 12 cycles; randomized, MRD–adapted consolidation and maintenance	TN; 18-70 y	46	75 PB/68 BM (best)	Confirmed MRD 30 mo, 95 (placebo)/100 (I) Unconfirmed MRD, 95 (I)/97 (I + V)
1L "Triplets"					
IVO,[74] n = 50	I + V + O, 14 cycles: O on d 1, 2, 8, and 15 of C1, then monthly for C2-7; I C2-14; V C3-14	TN and RR	32 (TN) 44 (RR)	BM: 67 (TN), 50 (RR)	NR
CLL2-GIVe,[75] n = 41	I + V + O, 15 cycles with response–adapted I maintenance: O, C1-6 I, C1-15; then maintenance if not in U-MRD CR; V, C1-12 (starting d22)	TN; high-risk: del(17p)/*TP53*mut	59	88 (PB-best)	79/93 (3 y)
CLL13 GAIA[76]	IVO, 12 cycles	TN, excluding patients with *TP53* aberrations	231	92 (PB)	91/96 (3 y)
AVO phase 2,[77,78] n = 61	AVO (A from C1; O cycles 2-7; V from C3). Duration 15/24 cycles, followed by MRD–adapted A maintenance beyond C24.	TN; cohort 1 (n = 37), all TN patients; cohort 2 (n = 31)	48	86 (BM-best)	93 (3 y)
BOVen, n = 50[79]	BOVen, 8-24 cycles MRD adapted	TN	57	96 (PB)/92 (BM)-best	NR
R/R "Doublets"					
M.D. Anderson phase 2,[80] n = 80	I + V, MRD–adapted I maintenance	R/R	NR	67 (24 m BM)	NR
TAP CLARITY,[67,81] n = 50	I + V, MRD response–adapted duration (maximum 36 cycles). I maintenance in MRD$^+$	R/R	78 (best)	64 (PB)/50 (BM)	78/91 (5 y)
HOVON141/Vision,[82] n = 225	I + V, MRD–adapted ibrutinib maintenance	R/R	64	50 (PB)/37 (BM)	98 (27 mo)

Treatment details: for the sake of space, the details of precombination BTKi monotherapy have not been included.
1L, first-line; A, acalabrutinib; AVO, acalabrutinib/venetoclax/obinutuzumab; BM, bone marrow; BOVen, Brukinsa (zanubrutinib)/obinutuzumab/venetoclax; C1, cycle 1; CR/CRi, complete remission with or without marrow recovery; FD, fixed duration; I, ibrutinib; IVO, ibrutinib-venetoclax-obinutuzumab; NR, no response; O, Obinutuzumab; PB, peripheral blood; TN, treatment-naïve; V, venetoclax.
*High-risk genomics: any of del(11q), del(17p), unmutated IgHV, or *TP53* mutation.

In contrast to patients receiving first-line CLL therapy, the outcomes for patients resistant to a covalent BTKi are poor, with a median PFS after venetoclax + rituximab therapy of only ~24 months,[86,87] even in patients without chemoimmunotherapy before BTKi therapy.[88] Although response rates to pirtobrutinib are high in this scenario, median PFS is only 19.6 months,[89] and patients frequently develop other mutations in *BTK* that drive resistance.[52] One approach to improving these outcomes is being evaluated in the BRUIN-322 study, which compares venetoclax + rituximab with pirtobrutinib + venetoclax + rituximab in a phase 3, registrational study (NCT04965493). The hope is that the combination of venetoclax with pirtobrutinib, 2 agents with different mechanisms of action, will suppress the selection of resistant clones (as has been seen in other studies of BTKi and venetoclax in R/R CLL) and thereby extend PFS.

Finally, we are entering an era in which immunotherapeutic approaches such as chimeric antigen receptor T cells and perhaps bispecific antibodies can achieve deep remissions and possible cure in patients with advanced B-cell lymphoproliferative disorders. The immunomodulatory effect of ibrutinib has been purported to enhance the efficacy of chimeric antigen receptor T cells,[87,90,91] and we expect to see novel combinations of BTKis and potent immunotherapeutic agents tested in upcoming trials.

Authorship

Contribution: C.T. and P.A.T. performed literature search and wrote the manuscript.

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ORCID profiles: C.T., 0000-0002-9759-5017; P.A.T., 0000-0003-2086-6031.

Correspondence: Constantine Tam, Department of Haematology, Alfred Hospital, Commercial Rd, Melbourne, VIC 3004, Australia; email: constantine.tam@alfred.org.au.

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