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Review

Selecting the optimal BTK inhibitor therapy in CLL: rationale and practical considerations

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***Abstract*:** Bruton's tyrosine kinase (BTK) inhibitors have dramatically changed the treatment of newly diagnosed and relapsed/refractory chronic lymphocytic leukemia (CLL). Ibrutinib, acalabrutinib, and zanubrutinib are Food and Drug Administration (FDA)-approved BTK inhibitors that have all demonstrated progression-free survival (PFS) benefit compared with chemoimmunotherapy. The efficacy of these agents compared to one another is under study; however, current data suggest they provide similar efficacy. Selectivity for BTK confers different adverse effect profiles, and longer follow-up and real-world use have characterized side effects over time. The choice of BTK inhibitor is largely patient-specific, and this review aims to highlight the differences among the agents and guide the choice of BTK inhibitor in clinical practice.

Keywords: Bruton's Tyrosine Kinase inhibitors, chronic lymphocytic leukemia

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Introduction

In the 1950s, Ogden C. Bruton, an American pediatrician, described an inherited immune-deficient state known as hypogammaglobulinemia in an 8-year-old boy, eventually culminating in the isolation of the gene that codes for Bruton's tyrosine kinase (BTK). This discovery was fundamental to our current understanding of chronic lymphocytic leukemia (CLL), a disease characterized by the uncontrolled proliferation of mature, but dysfunctional B cells. First understood as an inability to produce healthy antibody-producing cells, X-linked agammaglobulinemia (XLA) was the most common disease manifestation seen.[1] By the 1980s, with the advent of higher precision chromosomal marker linkage analysis, the *BTK* gene was isolated and was the 17th gene identified according to the Human Genome project.[2] This gene encodes a 659-amino acid-long tyrosine kinase, with a cysteine residue at position 481, crucial for the covalent bonds created with inhibitors used to treat CLL.[3] The function of this enzyme, Bruton's tyrosine kinase, a non-receptor member of the Tec kinase family, is vital for B-cell signaling, development, and differentiation and is a pre-requisite for B-cell survival and proliferation.[4] The activation, regulation, and role of BTK in tumor development is complex and not fully understood, but there is increasing evidence for its role in the transcriptional processes. A loss of function of *BTK* results in almost no production of mature B cells and premature cell death,[3] whereas a gain of function results in an immunosuppressed state due to malfunctioning B cells.

After the identification of BTK signaling as a pathway critical for oncogenesis in B-cell-associated malignancies, numerous murine studies were conducted utilizing various molecules in attempts to inhibit this pathway.[1,5] These studies found that inhibition of this pathway was likely to provide clinical benefit in B-cell malignancies, eventually leading to regulatory approval of a number of targeted agents. The first was ibrutinib, a therapy approved by the US Food and Drug Administration (FDA) for mantle cell lymphoma (MCL) in 2013. In addition to ibrutinib, acalabrutinib, approved in 2017 for MCL, followed by zanubrutinib for MCL in 2019, are the other commercially available BTK inhibitors

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currently on the market.[6] All three agents are mechanistically known to covalently and irreversibly bind to the cytosine-481 (C481) of BTK, blocking its ability to phosphorylate its substrates and subsequently suppressing downstream signaling. The newer agents, zanubrutinib and acalabrutinib, were found to have enhanced selectivity, thereby reducing off-target effects common with ibrutinib use.[7] Currently, newer BTK-targeted agents are in the pipeline for approval, such as pirtobrutinib, that work through non-covalent, reversible binding at alternative sites to the traditional C481 residue bound by covalent binding agents. For instance, pirtobrutinib functions primarily through the blockage of ATP-binding sites for BTK.[8] These alternative mechanisms provide pathways around resistance mutations associated with C481,[9] for example, C481S, as well as improved clinical tolerability compared to its older counterparts.

Now that ibrutinib is no longer the sole BTK inhibitor on the market for the treatment of CLL, clinicians are faced with the challenge of selecting the most appropriate BTK inhibitor, weighing the advantages and disadvantages of each. The data with BTK inhibitors and combinations with other agents is increasing exponentially. This review provides an overview of the large clinical trials evaluating the efficacy and safety of ibrutinib, acalabrutinib, zanubrutinib, and the early clinical data for pirtobrutinib, followed by combination therapies, such as with anti-CD20 monoclonal antibodies and venetoclax.

Efficacy of BTK inhibitors

Within the past decade, BTK inhibitors have caused a paradigm shift in the treatment of CLL. BTK inhibitors have demonstrated significant improvement in progression-free survival (PFS) and overall survival (OS) compared with traditionally used chemoimmunotherapy or alkylating agents.

Ibrutinib

Ibrutinib was the first BTK inhibitor brought to the clinical setting and was FDA approved first in 2013 for MCL and then in 2014 for the treatment of CLL in patients who had received at least one prior therapy.[10] Ibrutinib was first studied in a phase Ib/II trial in the relapsed or refractory setting.[11] Patients received either ibrutinib 420 or 840 mg once daily. The estimated PFS and OS at 26 months were 75% and 83%, respectively. Overall response rate (ORR) and BTK occupancy were similar at both dose levels, supporting the use of 420 mg daily in future studies. Notably, responses were seen among patients with standard- and high-risk CLL, including advanced-stage disease, a high number of previous therapies, and the presence of del17p.

The RESONATE study was a large phase III study evaluating the use of ibrutinib in the relapsed/refractory setting.[12] Nearly 400 patients were randomized to receive ibrutinib 420 mg daily or ofatumumab. Cross-over from ofatumumab to ibrutinib was allowed upon disease progression. Patients in the ibrutinib arm and the ofatumumab arm had received a median of 3 and 2 prior therapies, respectively, and approximately 50% of patients in both arms had high-risk cytogenetic abnormalities. At a median follow-up of 9.4 months, the median PFS had not been reached with ibrutinib, compared with 8.1 months with ofatumumab [hazard ratio (HR) = 0.22, $p < 0.001$]. In addition, the 12-month OS was significantly improved at 90% for ibrutinib and 81% with ofatumumab (HR = 0.43, $p = 0.005$). The ORR with ibrutinib was 43% (compared with 4% with ofatumumab; $p < 0.001$), with an additional 20% achieving a partial response with lymphocytosis (PR_L). The latter is a unique category of response in CLL to B-cell receptor pathway blockade, and results from 'redistribution' of CLL cells from the lymph nodes to the circulation because of impaired homing, where they eventually die due to the lack of microenvironmental signals.[13] The benefit of ibrutinib was seen regardless of high-risk disease features. On long-term follow-up, the superiority of ibrutinib remained.[14] After a median of 44 months, PFS had still not been reached for ibrutinib and was 8.1 months for ofatumumab (HR = 0.133, $p < 0.0001$) and 91% of patients randomized to the ofatumumab arm had experienced disease progression or death. The 3-year PFS rate was 59% with ibrutinib compared with 3% with ofatumumab. Response rates also increased with ibrutinib exposure over time with 91% achieving a response, with the majority of these being partial responses (PRs). In post hoc analyses, patients who had received greater than 2 prior therapies had shorter median PFS compared with those who received 2 or fewer prior therapies and those with *TP53* or *SF3B1*

mutations had a trend toward shorter PFS compared with those without these features.

Ibrutinib has since become a standard first-line treatment option, largely based on the phase III, randomized RESONATE-2 study. Newly diagnosed patients who were 65 years of age or older were randomized to receive ibrutinib or chlorambucil.[15] Cross over was allowed after progression on chlorambucil. After a median follow-up of 18.4 months, PFS had not been reached with ibrutinib compared with 18.9 months with chlorambucil (HR = 0.16, $p < 0.001$). OS was also significantly prolonged with ibrutinib. The 24-month estimated OS rate was 98% with ibrutinib and 85% with chlorambucil (HR = 0.16, $p = 0.001$). Improved PFS with ibrutinib was seen in high-risk subgroups such as those with Rai stage III or IV disease, del11q, and unmutated *IGHV* status, although of note, patients with del17p were excluded from this study. ORR was also significantly higher with ibrutinib compared with chlorambucil, with 86% of patients achieving a response with ibrutinib compared with 35% with chlorambucil. In the 5-year follow-up data, the median PFS had still not been reached in patients taking ibrutinib.[16] Five-year PFS and OS rates were 70% and 83% in the ibrutinib arm compared with 12% and 68% in the chlorambucil arm, respectively. PFS fell to 61% and OS to 78% at 6.5 years in patients receiving ibrutinib.[17] The median duration of treatment with ibrutinib was 57 months with 73%, 65%, and 27% of patients receiving therapy for more than 3, 4, and 5 years, respectively. Responses deepened over time. Cumulative complete response/complete response with incomplete count recovery (CR/CRi) was achieved in 11% of patients at the time of the initial analysis and improved to 30% after a median of 5 years and 34% after 6.5 years.

The German CLL11 study had showed that the addition of an anti-CD20 monoclonal antibody to chlorambucil significantly increased response rates and PFS in newly diagnosed patients with CLL and coexisting conditions.[18] An OS benefit was seen in patients receiving obinutuzumab with chlorambucil compared with chlorambucil alone, and thus, obinutuzumab added to chlorambucil emerged as a new 'standard' comparator in trials of patients with CLL and comorbidities. The phase III iLLUMINATE trial evaluated the combination of obinutuzumab with either ibrutinib or chlorambucil.[19] Newly diagnosed elderly or unfit patients were randomized to receive obinutuzumab plus ibrutinib or obinutuzumab plus chlorambucil. After a median follow-up of 31.3 months, median PFS had not been reached in the obinutuzumab plus ibrutinib arm, compared with 19 months in the obinutuzumab plus chlorambucil arm (HR = 0.23, $p < 0.0001$). The 30-month PFS rates were 79% and 31% in the obinutuzumab plus ibrutinib and the obinutuzumab plus chlorambucil arms, respectively. This PFS benefit was maintained in high-risk subgroups such as del17p, *TP53* mutation, del11q, and unmutated *IGHV*. ORR was also significantly greater in patients receiving obinutuzumab plus ibrutinib (88% *versus* 73%, $p = 0.0035$). Median OS had not been reached in either group at the time of the analysis.

Chlorambucil-based regimens produce poor outcomes; however, chemoimmunotherapy still remains an option. In the phase III Alliance A041202 trial, ibrutinib was compared with the chemoimmunotherapy regimen, bendamustine plus rituximab (BR).[20] Patients with newly diagnosed CLL 65 years of age or older were randomized to receive BR, ibrutinib monotherapy, or ibrutinib plus rituximab. The 2-year estimated PFS rates were 74% with BR, 87% with ibrutinib monotherapy (HR = 0.39, $p < 0.001$), and 88% with ibrutinib plus rituximab (HR = 0.38, $p < 0.001$), both comparisons (of the ibrutinib-containing arms) being to BR. There was no difference between the ibrutinib monotherapy arm and the ibrutinib plus rituximab arm with regard to PFS. ORRs were higher in the ibrutinib-containing arms compared with the BR arm; however, complete response (CR) rates and rates of minimal residual disease (MRD) negativity were numerically higher with BR. This is consistent with most responses to ibrutinib being PRs.[21,22]

The above frontline trials evaluated ibrutinib in the elderly population. The E1912 trial compared ibrutinib in combination with rituximab to standard of care chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) in patients aged 70 or younger.[23] Three-year PFS rates were 89% with ibrutinib plus rituximab and 73% with FCR (HR = 0.35, $p < 0.001$). An OS advantage was seen for ibrutinib plus rituximab as well. Three-year OS rates were 99% and 92% for ibrutinib plus rituximab compared with FCR (HR = 0.17, $p < 0.001$). In a subgroup analysis of patients with mutated *IGHV* in whom FCR

would potentially have been preferred,[24,25] the PFS rates were similar between both arms.

Acalabrutinib

The next BTK inhibitor developed was acalabrutinib. It was first FDA approved in 2017 for relapsed or refractory MCL, but later gained approval for CLL in 2019, largely based on the ASCEND and ELEVATE-TN trials.[26] The ASCEND trial compared acalabrutinib with investigator's choice (idelalisib plus rituximab or BR) in patients with relapsed or refractory CLL.[27] Patients had received a median of two prior lines of therapy. Median PFS was not reached in the acalabrutinib arm and was 16.5 months with investigator's choice (HR = 0.31, $p < 0.0001$) after a median follow-up of 16.1 months. The estimated 1-year PFS was 88% and 68% in the acalabrutinib and investigator's choice arms, respectively. This benefit was maintained among those with high-risk features. There was no difference in OS. After 3 years of follow-up, the median PFS had still not been reached and the 36-month PFS rate was 63%, establishing the efficacy and durability of response with acalabrutinib in the relapsed or refractory setting.[28]

In the ELEVATE-TN trial, patients aged 65 years of age or older with newly diagnosed CLL were randomized to receive acalabrutinib monotherapy, acalabrutinib plus obinutuzumab, or obinutuzumab plus chlorambucil.[29] After a median follow-up of 28.3 months, the median PFS had not been reached in either acalabrutinib-containing arm, compared with 22.6 months with obinutuzumab plus chlorambucil (HR = 0.1 for obinutuzumab plus acalabrutinib *versus* obinutuzumab plus chlorambucil, $p < 0.0001$; HR = 0.2 for acalabrutinib monotherapy *versus* obinutuzumab plus chlorambucil, $p < 0.0001$). The estimated 2-year PFS rate was 93% with obinutuzumab plus acalabrutinib, 87% with acalabrutinib monotherapy, and 47% with obinutuzumab plus chlorambucil. The PFS benefit was observed in patients with high-risk features such as later stage disease, del17p or *TP53* mutation, del11q, unmutated *IGHV*, and complex cytogenetics. Upon long-term follow-up, after a median of 47 months, the median PFS had still not been reached in either acalabrutinib-containing arm, and 4-year estimated PFS rates were 87%, 78%, and 25% for obinutuzumab plus acalabrutinib, acalabrutinib monotherapy, and obinutuzumab plus chlorambucil, respectively.[30] There was a trend toward an OS benefit with obinutuzumab plus acalabrutinib compared with obinutuzumab plus chlorambucil; however, it did not reach statistical significance ($p = 0.0604$).

Notably, the efficacy of acalabrutinib has been established in patients who were intolerant to ibrutinib. In a phase II study in patients with relapsed or refractory CLL, patients intolerant to ibrutinib received acalabrutinib at the FDA-approved dose of 100 mg twice daily.[31] Patients were deemed intolerant to ibrutinib if they had experienced persistent grade 3 or 4 adverse events or had persistent or recurrent grade 2 adverse events despite dose modification and interruption. Patients had to have met the International Workshop on CLL 2008 criteria for progressive disease after stopping ibrutinib and could not have received another therapy prior to starting acalabrutinib. Patients had received a median of two prior lines of therapy (including ibrutinib). Median PFS was not reached; however, the 36-month estimated PFS was 58%. The ORR was 73% and improved to 78% when including patients with PR_L. The estimated proportion of patients with a 36-month duration of response was 65%. Among the cohort, 27% of patients started subsequent treatment after acalabrutinib with a median time to next treatment of 44 months. This demonstrates that acalabrutinib can be a viable treatment option in those patients that are intolerant to ibrutinib.

Zanubrutinib

Zanubrutinib was next developed and is currently FDA approved for relapsed or refractory MCL, Waldenström's macroglobulinemia, and relapsed or refractory marginal zone lymphoma.[32] It is not FDA approved for CLL; however, it is a recommended treatment option in the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of both newly diagnosed and relapsed and refractory CLL.[33]

The ALPINE trial was a large, phase III, randomized trial of patients with relapsed or refractory CLL or small lymphocytic leukemia (SLL).[34] Over 400 patients were randomized to receive zanubrutinib or ibrutinib. The ORR after a median of 15 months was significantly higher with zanubrutinib compared with ibrutinib (78% *versus* 63%, $p = 0.0006$). The estimated 12-month

PFS rates were 95% and 84% with zanubrutinib and ibrutinib, respectively ($p = 0.0007$). Although the follow-up is short, the ALPINE trial shows the efficacy of zanubrutinib in the relapsed/refractory CLL population.

Zanubrutinib was also studied in the multi-arm SEQUOIA trial. Arm C of the trial was a nonrandomized cohort of newly diagnosed elderly patients with CLL with confirmed del17p.[35] Notably, patients with cardiovascular disease or those on anticoagulation were included in the study. After a median of 18.2 months, the estimated 18-month PFS rate was 89%, and the ORR was 95%. Duration of response was maintained for at least 12 months in 93% of patients.

In the SEQUOIA trial arms enrolling patients without del17p, patients were randomized to receive zanubrutinib or BR.[36] After a median of 26.2 months of follow-up, PFS significantly favored zanubrutinib (HR = 0.42, $p < 0.0001$). Estimated 24-month PFS rates were 86% with zanubrutinib compared with 70% with BR. ORR was greater for zanubrutinib (95% *versus* 85%); however, as with ibrutinib,[20] more complete responses were seen with chemoimmunotherapy.

Pirtobrutinib

Pirtobrutinib (LOXO-305) is a novel, non-covalent, reversible BTK inhibitor currently in clinical trials and exhibits activity in C481-mutated disease, a common mechanism of resistance to covalent BTK inhibitors in CLL.[8,37] The BRUIN trial was a phase I/II dose finding study evaluating pirtobrutinib in over 300 patients with relapsed or refractory B-cell malignancies, including CLL, SLL, and MCL.[38] Patients with CLL or SLL had received a median of three lines of prior therapy and 86% had received a prior BTK inhibitor. Among patients with CLL and SLL who had received a previous covalent (irreversible) BTK inhibitor, the ORR with pirtobrutinib was 62%. Of these, the ORRs in patients previously intolerant and previously resistant to BTK inhibitors were 52% and 67%, respectively. Notably, those with documented C481-mutant disease achieved an ORR of 71%. Based on this trial, the recommended phase II dose was determined to be 200 mg once daily and is being evaluated in further clinical trials. In a press release from Loxo Oncology (now Eli Lilly), the median PFS for those previously treated with a BTK inhibitor had not been reached after a median of 9.4 months of follow-up.[39] Pirtobrutinib may represent an effective new therapeutic option in a heavily pretreated patient population, circumventing the problem of C481 and similar BTK mutations, but resistance mechanisms to it, too, have very recently been described.[40]

BTK inhibitor-based combination therapies

Since the advent of BTK inhibitors, multiple studies combining these agents with chemoimmunotherapy and other highly effective therapies, such as the B-cell lymphoma 2 (BCL-2) antagonist venetoclax, have been conducted.

The HELIOS trial was a phase III, placebo-controlled trial evaluating the efficacy of adding ibrutinib or placebo to BR in the relapsed and refractory setting.[41] Patients must have received at least one previous line of systemic therapy consisting of at least two cycles of a chemotherapy-containing regimen. Patients with del17p were excluded due to their poor response to chemoimmunotherapy. Ibrutinib or placebo was continued until disease progression or unacceptable toxicity; however, crossover to ibrutinib was allowed after progression on BR plus placebo. Patients in both groups had received a median of two prior lines of therapy with the most common regimen being FCR. The trial was stopped early due to the PFS benefit seen with ibrutinib. After a median follow-up of 17 months, PFS in the ibrutinib-containing group had not yet been reached, compared with 13.3 months in the BR plus placebo group (HR = 0.2, $p < 0.0001$). Estimated rates of PFS at 18 months were 79% and 24% in the ibrutinib- and placebo-containing arms, respectively. After adjusting for crossover, OS was significantly longer in patients receiving ibrutinib compared with those receiving placebo (HR = 0.577, $p = 0.033$). ORR was significantly higher in the ibrutinib-containing than placebo-containing arms (83% *versus* 68%) and more patients in the ibrutinib arm were able to achieve MRD negativity. After 5 years of follow-up, the median investigator-assessed PFS was 65.1 months in the ibrutinib plus BR arm and 14.3 months in the placebo plus BR arm.[42] Responses deepened over time on ibrutinib with CR/CRi rates improving from 21.5% at the interim analysis to 40.8% at the final 5-year analysis. In addition, an OS benefit was seen with ibrutinib plus BR, despite 63% of patients in the placebo plus BR arm crossing

over to ibrutinib. However, this regimen (ibrutinib plus BR) is not commonly used, unless rapid debulking is necessary, and most ibrutinib use is as monotherapy, given also the lack of PFS or OS benefit for the addition of rituximab.[9,43]

Although its use is largely being replaced by targeted therapies (based on, for example, the PFS and OS benefits observed for ibrutinib plus rituximab over FCR in the E1912 trial), chemoimmunotherapy with FCR could be considered in the front line setting in younger, fit patients with mutated *IGHV* and favorable karyotype [i.e. no del17p or del11q on fluorescence *in situ* hybridization (FISH)] based on high rates of response and durable treatment-free remissions.[24,33,44,45] A phase II trial aimed to evaluate whether adding ibrutinib to fludarabine and cyclophosphamide, and replacing rituximab with obinutuzumab (iFCG), would yield deeper and durable responses while limiting exposure to chemoimmunotherapy and employing finite duration ibrutinib.[46] Patients received three cycles of iFCG. Patients who achieved CR/CRi and MRD negativity in the bone marrow continued obinutuzumab for three more cycles and ibrutinib for nine more cycles. All other patients received nine additional cycles of obinutuzumab plus ibrutinib. Patients who achieved MRD negativity at the end of 12 cycles discontinued all treatment, including ibrutinib, and those who remained MRD positive continued on single agent ibrutinib. After a median of 41.3 months of follow-up, 38% of patients had achieved CR/CRi and 87% had achieved MRD negativity after 3 months. After 12 months of therapy, 98% of patients had achieved MRD negativity in the bone marrow. Three-year PFS and OS rates were 98% and 98%, respectively.

A chemotherapy-free regimen recently studied is the combination of ibrutinib and venetoclax. In an investigator-initiated phase II study, patients with high risk (del17p, *TP53* mutation, del11q, unmutated *IGHV*, or age 65 years or older) received ibrutinib monotherapy for three cycles.[47] Starting in cycle 4, venetoclax was added using the standard ramp-up and combined therapy was given for 24 cycles. After 12 cycles, 88% of previously untreated patients achieved CR/CRi and 61% achieved MRD negativity in the bone marrow. The depth of remission improved over time. After completion of 24 cycles of therapy, 66% had achieved MRD negativity in the bone marrow, 16% had low MRD-positive response, 1% had high MRD-positive response, and 16% had discontinued therapy prior to the cycle 24 assessment.[48] Estimated 3-year PFS and OS rates were 93% and 96%, respectively. In the phase II CAPTIVATE trial, newly diagnosed CLL patients received 3 cycles of ibrutinib followed by 12 cycles of ibrutinib plus venetoclax.[49] Patients who achieved undetectable MRD (uMRD) in both peripheral blood and bone marrow were then randomly assigned to received placebo or ibrutinib until MRD relapse or disease progression. Those who had detectable disease (uMRD not confirmed population) were randomly assigned to open-label ibrutinib or ibrutinib plus venetoclax (2-year maximum duration of venetoclax). After 12 cycles of combined ibrutinib plus venetoclax, 58% of patients eligible for random assignment achieved uMRD in both peripheral blood and bone marrow and were then randomly assigned to placebo or ibrutinib. After a median follow-up of 31.3 months, there was no significant difference in 1-year disease-free survival (DFS) rates between those receiving placebo *versus* ibrutinib (95% *versus* 100%, $p=0.15$). Estimated 30-month PFS rates were 95% and 100% with placebo and ibrutinib, respectively. The rate of uMRD in the peripheral blood 12 cycles after randomization to placebo or ibrutinib was 84% with placebo and 77% with ibrutinib. The similar rates of 1-year DFS, 30-month PFS, and uMRD in the peripheral blood at 12 cycles support time-limited therapy in those that achieve uMRD with combination therapy; however, follow-up remains short. In the cohort where uMRD was not confirmed after the initial 12 cycles of ibrutinib plus venetoclax, the estimated 30-month PFS rates were 95% with ibrutinib and 97% with ibrutinib plus venetoclax. The CAPTIVATE trial provides further support for fixed duration therapy with ibrutinib when given in combination with venetoclax and provides additional data that may inform how to tailor treatment based on MRD detectability.

Arm D of the SEQUOIA trial evaluated the efficacy of combining zanubrutinib with venetoclax in the newly diagnosed population with del17p.[50] Zanubrutinib was administered twice daily for 3 cycles followed by 12–24 cycles of zanubrutinib combined with venetoclax. Combination treatment was stopped after 24 cycles or if uMRD at a level of 10^{-4} was achieved, whichever came first.

The median follow-up duration was 11.2 months for efficacy; the ORR was 97% for patients who had reached the initial efficacy assessment. One patient had experienced progressive disease at the data cutoff; however, the results are preliminary, and follow-up remains short.

The GLOW study is a phase III trial comparing fixed duration ibrutinib plus venetoclax to chemoimmunotherapy with obinutuzumab plus chlorambucil in elderly patients or those with comorbidities with newly diagnosed CLL.[51] Patients with del17p or *TP53* mutations were excluded. Patients received 3 cycles of ibrutinib monotherapy followed by 12 cycles of ibrutinib plus venetoclax and then discontinued all therapy. In the primary analysis after a median follow-up of 27.7 months, PFS had not been reached for ibrutinib plus venetoclax and was 21 months for obinutuzumab plus chlorambucil (HR = 0.216, $p < 0.0001$). The MRD negativity rate in the bone marrow 3 months after stopping therapy was significantly higher in the ibrutinib plus venetoclax arm (52% *versus* 17%), and 85% of these patients maintained MRD negativity in the peripheral blood 12 months after treatment completion.

The most recent combination to be studied is the triple combination of a BTK inhibitor plus venetoclax plus an anti-CD20 monoclonal antibody. Obinutuzumab has largely replaced rituximab due to its increased capacity for causing antibody-dependent cellular cytotoxicity and apoptosis.[18]

Fifty patients with either newly diagnosed or relapsed/refractory CLL were given a time-limited combination regimen containing obinutuzumab, ibrutinib, and venetoclax for a total of 14 cycles.[52] The CR with uMRD (in blood and bone marrow) rate 2 months after completion of treatment was 28% in both the treatment naïve and relapsed/refractory groups. After almost 2 years of follow-up, the median PFS had not been reached in either group.

Following a similar trial design, acalabrutinib was combined with venetoclax and obinutuzumab in 37 patients with newly diagnosed CLL.[53] Acalabrutinib was given as monotherapy for one cycle and then combined with obinutuzumab for six cycles. Starting in cycle 4, venetoclax was introduced with an accelerated ramp up and continued for a combined acalabrutinib and venetoclax duration of 12–24 cycles. If patients achieved uMRD in the bone marrow, they could discontinue all treatment at the start of cycle 16 (if in CR) or cycle 25 (if in PR). After a median of 27.6 months, 38% of patients had achieved a CR with uMRD in the bone marrow at the assessment prior to starting cycle 16. Rates of uMRD in the blood and bone marrow (regardless of response status) were 68% and 46%, 86% and 86%, and 89% and 86% at the cycle 8, cycle 16, and cycle 25 assessments, respectively. Another phase II trial is ongoing to investigate the effect of acalabrutinib plus venetoclax with or without early obinutuzumab in patients with high-risk CLL or those with relapsed or refractory disease (NCT04169737).

Zanubrutinib has also been studied in such a 'triplet'.[54] Newly diagnosed patients received zanubrutinib monotherapy for 1 month and then obinutuzumab in cycles 2–8. Venetoclax was started in cycle 3 and continued for 8–24 cycles depending on achievement of uMRD in the blood and bone marrow. Among these patients, 89% of patients achieved uMRD in both the blood and bone marrow after a median of 25.8 months. The median time to uMRD in the bone marrow was 8 months. In patients who had stopped treatment, 94% still maintained uMRD in the blood after a median of 15.8 months post-treatment discontinuation. Only one patient experienced disease progression.

Safety

In general, a major contributor to agent selection for any disease state is the anticipated side effects. These considerations often become the rate-limiting step to successful outcomes of therapy. Each patient is unique in terms of their comorbidities, concomitant medications, and patterns of drug metabolism. Even with the understanding we have of CLL pathophysiology and the role BTK plays, there is still a lot left to learn about what off-target effects an agent can cause, and what predisposes a given patient to the risk of experiencing those undesirable outcomes.

It is well known that BTK inhibitors have off-target effects, resulting in a plethora of unique adverse events.[55] The inhibition of epidermal growth factor receptor (EGFR) is associated with diarrhea and dermatological effects, such as rash.[56] BTK inhibition, along with inhibition of other Tec family kinases, results in platelet inhibition, predisposing to bleeding. Finally, cardiac arrhythmias have been

associated with inhibition of C-terminal Src kinase (CSK). One goal of developing new BTK inhibitors is to reduce these off-target effects, thereby increasing the safety parameters around BTK inhibitor therapy.

BTK is a regulator of innate immunity as well, specifically influencing the role of pathogen recognition by Toll-like receptors. Thus, when BTK is inhibited, it results in an environment that predisposes to opportunistic infections.[57,58] Invasive fungal infections, namely *Aspergillus*, have been found to be associated with the use of BTK inhibitors. In the cases described, a number of confounding factors may have contributed to the increased risk of invasive fungal infections. Some of these included neutropenia, steroid administration, and heavy pre-treatment, all of which are independent risk factors for invasive fungal infections. In this case series, invasive fungal infections presented within a median of 3 months of therapy.[59] Therefore, it is felt that antifungal prophylaxis is not necessarily warranted, but close monitoring at the initiation of therapy, especially in those with any of the aforementioned risk factors, is highly recommended.

In addition to increased infection risk, the use of BTK inhibitors has also been found to decrease seroconversion of patients receiving vaccines. In one study, patients receiving ibrutinib and the standard dose influenza vaccine had seroconversion rates as low as 7% and, in another study, as low as 26% when administered the higher dose influenza vaccine.[60,61] CLL patients are known to have an underlying humoral deficiency due to the baseline malfunction of B cells. In a study conducted by Pleyer *et al.*, when comparing untreated CLL patients with those on BTK inhibitors, responses to hepatitis B vaccines (HepB-CpG) were drastically different. Treatment-naive patients with CLL experienced an antibody response in 28% of cases, as opposed to the individuals receiving BTK inhibitors having a response rate of only 3.8%.[62] Given the current COVID-19 pandemic, an obvious question that arises is what the efficacy of the vaccines in this patient population is.[63] Although a large amount of data has not been published, it is well established that these patients have difficulty mounting an adequate response, especially those receiving BTK inhibitors.[64,65]

The incidence of bleeding with the use of ibrutinib therapy warrants concern and attention. In a systematic meta-analysis of ibrutinib studies, the incidence of bleeding of any kind was 20.8 per 100 patient-years.[66] In a different, single-center, retrospective review, bleeding of any grade occurred in 50.6% of patients.[67] At baseline, untreated XLA patients do not have a predisposition to bleeding, which further implicates pharmacologic BTK inhibition in the pathogenesis of bleeding with ibrutinib use.[68,69] Being a member of the Tec kinase family, BTK functions to signal downstream of various platelet transmembrane receptors that are irreversibly inhibited with the administration of agents such as ibrutinib.[70] This effect has been found to be dose dependent, correlating clinically with bleeding.[71]

As mentioned earlier, cardiac manifestations, namely arrhythmias, have been associated with the inhibition of CSK. It has been postulated that dysfunction within the cardiomyocytes due to reduced gap junctional communication occurs with the inhibition of CSK.[72] The most common manifestation of this is atrial fibrillation.[73,74] A more severe form of arrhythmia, ventricular arrhythmias, resulting in sudden death has also been reported in very small numbers.[75] Rather than the CSK pathway though, ventricular arrhythmias may be due to some element of direct hERG-channel or phosphoinositide-3-kinase inhibition as well.[76] However, in a review by Brown *et al.*,[73] it was found that patients diagnosed with CLL over the age of 65 years had a baseline incidence of atrial fibrillation of 6%, higher than in the age-matched general population (1–1.8%). Standard atrial fibrillation therapy includes rate control, usually with a beta blocker, in addition to stroke prevention therapy with anticoagulation (based on an appropriate CHA_2DS_2-VASc score). It should be noted that in the Brown *et al.* review, all patients with appropriate CHA_2DS_2-VASc scores were placed on anticoagulation, resulting in only one bleeding-related death. With the concern of increased bleeding associated with BTK inhibitor therapy, the risk *versus* benefit ratio must be assessed prior to administering this combination in patients.

Hypertension is an additional cardiotoxicity that has been shown to manifest with BTK inhibitor therapy. A follow-up analysis of the first ibrutinib study found a 28% incidence of hypertension.[21] In a more recent, single-center, retrospective analysis of 562 patients on ibrutinib therapy, the incidence of new or worsened hypertension was

78.3%, with 17.7% of patients having new-onset hypertension. The mechanism behind the hypertension is loosely understood, but accumulating data points toward inhibition of the phosphoinositide 3-kinase pathway.[77] Another hypothesized mechanism is due to decreased nitric oxide formation secondary to vascular endothelial growth factor down-regulation seen with BTK inhibition.[78] No single anti-hypertensive agent has been found to be more beneficial than another for the treatment of BTK inhibitor-associated hypertension.[79]

In a real-world analysis of 616 patients treated with ibrutinib therapy, after a median follow-up of 17 months, approximately 41% of patients discontinued therapy. Therapy was not discontinued due to disease progression in most cases, but rather intolerance.[80] Newer agents like acalabrutinib and zanubrutinib, which are more selective for BTK, have entered the market due to their decreased off-target activity and therefore increased tolerability.

The ELEVATE-RR study compared acalabrutinib with ibrutinib in relapsed and refractory CLL patients in a phase III randomized trial.[81] Acalabrutinib's efficacy was non-inferior to that of ibrutinib, but the major finding of this study was the difference in adverse event profiles. All-grade atrial fibrillation incidence was 9.4% with acalabrutinib, compared with 16% with ibrutinib ($p = 0.02$). Zanubrutinib was studied in the same population and compared with ibrutinib in the ALPINE phase III randomized trial.[34] In an interim analysis, zanubrutinib showed a superior response rate compared with ibrutinib, as well as improved PFS. The incidence of all-grade atrial fibrillation was also less with zanubrutinib at 2.5% compared with 10.1% with ibrutinib ($p = 0.0014$). Rates of bleeding, discontinuation due to adverse events, and death were all less with zanubrutinib than with ibrutinib as well. The major consequence of this is that a decreased incidence of atrial fibrillation translates to a decreased need for anticoagulation therapy and therefore a decreased compounding of bleeding risk with BTK inhibition.

BTK inhibition, though immensely beneficial in CLL therapy, has its own risks. Increased bleeding risk due to the inhibition of platelet function, along with the increased need for anticoagulation therapy for stroke prevention due to the risk of atrial fibrillation, hypertension, and the risk of invasive fungal infections, all are important caveats when assessing the best choice of therapy. Intricate assessment of patient-specific needs and comorbidities, along with close patient follow-up, especially within the first few months of therapy, can help mitigate some of these concerns.

The choice of BTK inhibitor

Selection of the appropriate BTK inhibitor is multifactorial and depends on side effect profile, comorbidities of the patient, concomitant medications and potential drug–drug interactions, cost, ease of administration, and desired outcomes of therapy.

Ibrutinib is the least selective of the BTK inhibitors, and its off-target effects lead to an increased incidence of adverse events, particular cardiovascular adverse events. In the 7-year follow-up of the RESONATE-2 trial, few adverse events were seen in years 5–7.[17] In the ELEVATE-RR and the ALPINE trials, fewer adverse effects with acalabrutinib and zanubrutinib were observed than in patients receiving ibrutinib, with the exception of headache for acalabrutinib and neutropenia for zanubrutinib.[34,81] Certain disease-related factors may influence the choice of a BTK inhibitor. In the ELEVATE-TN and ELEVATE-RR studies, patients with significant cardiovascular disease and those taking vitamin K antagonists were excluded.[29] However, in the SEQUOIA trial, those with cardiovascular disease and those receiving anticoagulation were allowed to enroll.[35] Due to lower rates of atrial fibrillation/flutter and hypertension, acalabrutinib or zanubrutinib may be favored over ibrutinib in patients with pre-existing cardiovascular disease. Although rates of hemorrhage were lower for acalabrutinib than ibrutinib in the ELEVATE-RR trial, patients already on anticoagulation were excluded. Zanubrutinib could be considered for those at risk for major bleeds, such as patients on concomitant anticoagulation or antiplatelet therapy, as the SEQUOIA trial demonstrated safety in this population. Currently, zanubrutinib has not been studied head-to-head against acalabrutinib in the relapsed/refractory or newly diagnosed setting.

All three available BTK inhibitors exhibit drug–drug interactions. All undergo hepatic metabolism, primarily through CYP3A4, which has implications for drug–drug interactions.[10,26,32] Ibrutinib has the most tablet or capsule strengths

available and has manufacturer-recommended dose modifications for those taking moderate or strong CYP3A inhibitors. Acalabrutinib and zanubrutinib, however, only come in one capsule strength each and have limited recommendations regarding concomitant CYP3A inhibitors. It is recommended to avoid acalabrutinib and dose reduce zanubrutinib to 80 mg once daily with strong CYP3A inhibitors. In addition, the solubility of acalabrutinib decreases with increasing gastric pH. Acalabrutinib should not be administered with concomitant proton pump inhibitors and needs to be administered 2 hours prior to taking an H2-receptor antagonist and separated by 2 hours from antacids. A new intermediate-release film-coated tablet of acalabrutinib is being studied that produces similar pharmacokinetic data when administered with proton pump inhibitors;[82] however, in patients with gastrointestinal conditions that require proton pump inhibitor therapy, the FDA-approved acalabrutinib capsule should be avoided. Ibrutinib and zanubrutinib can be taken without regard to acid-lowering therapy. Ease of administration should also be considered, as adherence affects BTK occupancy and therefore could impact efficacy. Ibrutinib is a once daily medication while acalabrutinib requires twice daily administration. Zanubrutinib was studied as a twice daily drug; however, manufacturer and NCCN recommendations suggest that once daily administration can be considered.

All three BTK inhibitors on the market are available as brand-only medications and come at a significant cost, as BTK monotherapy is typically continued indefinitely, until disease progression or intolerable toxicity. This is because of the limited ability of BTK inhibitor monotherapy to eradicate MRD.[21,22] This and other considerations have led to interest in time-limited or finite duration regimens, such as those of venetoclax with an anti-CD20 monoclonal antibody,[83,84] or venetoclax with ibrutinib.[48,49] Another promising strategy has been the addition of venetoclax in patients on ibrutinib to induce MRD eradication.[85] Ibrutinib will be the first BTK inhibitor to have a generic version on the market; however, this is not expected until 2032.

Disease-related factors may impact BTK inhibitor selection as well. Recent data suggest that, in patients with del17p or *TP53* mutations, BTK inhibitor therapy may produce durable responses.[86–88] In a pooled analysis of 89 newly diagnosed patients with *TP53* aberrations, the 4-year PFS rate was 79% when treated with ibrutinib or ibrutinib with an anti-CD20 monoclonal antibody. Although not compared head-to-head, these data appear to be stronger than with other strategies. In the CLL14 trial evaluating venetoclax combined with obinutuzumab, the 4-year PFS rate was 53% in patients with *TP53* mutations.[89] Zanubrutinib was studied specifically in the population with del17p and exhibited robust responses; however, follow-up is short.[35] More data is needed to see if the improved PFS is because of continued therapy, or if BTK inhibition is truly a more effective strategy in the *TP53*-mutated and del17p population. Finally, in patients who exhibit resistance to FDA-approved BTK inhibitors, specifically those due to a C481 mutation, enrollment in clinical trials with pirtobrutinib is an effective approach with a favorable adverse effect profile.[38]

The question of the importance, or lack thereof, of the anti-CD20 monoclonal antibody in the setting of BTK inhibitor therapy remains. In the CLL11 trial, the addition of an anti-CD20 monoclonal antibody to chlorambucil provided not only a PFS benefit but also an OS benefit in newly diagnosed patients with pre-existing comorbidities.[18] However, chlorambucil alone leads to inferior outcomes compared with BTK inhibitors[15] and has largely fallen out of favor as a treatment option. Obinutuzumab plus chlorambucil outperformed rituximab plus chlorambucil, with a median PFS of 28.9 months compared with 15.7 months (HR = 0.49, $p < 0.0001$) and a median OS that was not reached compared with 73.1 months (HR = 0.76, $p = 0.0245$), after 5 years of follow-up.[90] These results have made obinutuzumab the preferred anti-CD20 monoclonal antibody.

In a single-center study comparing ibrutinib with ibrutinib plus rituximab in both newly diagnosed and relapsed/refractory CLL, the combination did not show an improvement in PFS after a median follow-up of 36 months.[43] Time to normalization of peripheral blood lymphocytes (rituximab blunts the redistribution lymphocytosis caused by ibrutinib) and time to CR was shorter with ibrutinib plus rituximab. In the Alliance A0141202 trial comparing single agent ibrutinib with ibrutinib plus rituximab and BR, there was no difference in PFS or OS when rituximab was added to ibrutinib.[20] In the ELEVATE-TN trial, the estimated 2-year PFS

rates between acalabrutinib plus obinutuzumab and acalabrutinib monotherapy were similar.[29] After 4 years of follow-up, the estimated PFS rates were numerically higher with acalabrutinib plus obinutuzumab compared with acalabrutinib monotherapy (87% *versus* 78%), although the study was not powered to detect a difference in PFS between these two arms.[91] There was a trend toward an OS benefit with the addition of obinutuzumab, although this was not statistically significant. More patients were likely to achieve CR/CRi with acalabrutinib plus obinutuzumab compared with acalabrutinib alone (31% *versus* 11%). Importantly, the addition of the monoclonal antibody can increase rates of adverse events, particularly neutropenia.

Future studies and agents

A number of agents that target the BTK signaling cascade are in the pipeline to continue to broaden safe and effective therapy options for patients with CLL. ARQ-531, a reversible, non-covalent BTK inhibitor like pirtobrutinib, recently completed a phase I dose escalation study, showing activity in patients resistant to covalent BTK inhibitors by reversibly suppressing oncogenic BCR signaling.[92] Vecabrutinib is another non-covalent, reversible BTK inhibitor in ongoing phase I studies.[93] The expectation for this agent is that due to the reversible and non-covalent nature of its binding, it should have less off-target activity, thereby increasing tolerability, as well as efficacy in the face of C481 active site mutations. A new agent, CG-806, a first in class pan-*fms*-like tyrosine kinase 3 (*FLT3*)/pan-BTK inhibitor, has been studied *ex vivo* on peripheral blood samples from CLL patients, and was shown to broadly inhibit BCR signaling, resulting in apoptosis of the cells.[94] With the rise in BTK therapy utilization in CLL patients and the coincident risk of the emergence of new escape pathways, it is necessary to continually assess and expand our therapeutic arsenal to overcome this barrier, while maintaining efficacy and tolerability.

Conclusion

BTK inhibitors have vastly changed the landscape of treatment of CLL. The choice of BTK inhibitor relies on patient- and drug-specific factors such as comorbidities, concomitant medications, cost, and side-effect profiles. Acalabrutinib and zanubrutinib have a more favorable side-effect profile due to their increased selectivity for the BTK kinase. Efficacy of these agents is overall similar, with early data suggesting zanubrutinib may have a PFS benefit over ibrutinib in the relapsed/refractory setting. To date, there has been no significant OS advantage demonstrated between the BTK inhibitors; however, longer follow-up is needed. The addition of anti-CD20 monoclonal antibodies remains controversial. The data currently does not demonstrate significant PFS or OS benefits; however, this may be considered in patients with bulky disease in whom rapid debulking would be beneficial. Obinutuzumab may have advantages over rituximab in this regard. Combinations of BTK inhibitors with other small molecule inhibitors such as venetoclax have shown promising results in phase II trials and are opening up the possibility of time-limited therapy aimed at MRD eradication. Overall, BTK inhibitors offer CLL patients an effective, oral, generally well-tolerated, and chemotherapy-free treatment option and will likely continue to be major players in the CLL treatment landscape for the foreseeable future.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors.

Author contributions

Alexandra R. Lovell: Data curation; Writing – original draft.

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