

# BTK Inhibition and Treatment Options in Chronic Lymphocytic Leukemia



**Susan M. O'Brien, MD**  
 University of California, Irvine  
 Orange, CA



**Alexey Danilov, MD, PhD**  
 City of Hope  
 Duarte, CA



**Seema Ali Bhat, MD**  
 The Ohio State University Comprehensive  
 Cancer Center—The James  
 Columbus, OH



**Catherine C. Coombs, MD**  
 University of California, Irvine  
 Orange, CA



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**A**t an *Around the Practice*<sup>®</sup> program hosted by CancerNetwork<sup>®</sup>, a panel of experts discussed the past, present, and future of Bruton tyrosine kinase (BTK) inhibition in the treatment of chronic lymphocytic leukemia (CLL). The discussion was led by **Susan M. O'Brien, MD**, a professor in the Division of Hematology and Oncology at the University of California, Irvine.

The panelists included **Alexey Danilov, MD, PhD**, professor and associate director of the Toni Stephenson Lymphoma Center at City of Hope in Duarte, California; **Seema Ali Bhat, MD**, assistant professor at the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute of The Ohio State University Comprehensive Cancer Center—The James in Columbus, Ohio; and **Catherine C. Coombs, MD**, an associate professor in the Division of Hematology and Oncology at the University of California, Irvine.

## The State of the Disease

**O'BRIEN:** CLL is the most common leukemia in adults in the Western world. Everybody in a broad oncology practice will have some experience providing care for patients with CLL because they're

so common. Many patients present without any symptoms. That's probably more common than presenting *with* symptoms. Nowadays it's very common for a patient to [receive a diagnosis] after a routine physical, with a complete blood count showing an elevated lymphocyte count. Usually, [a clinician will assume it's] CLL until proved otherwise.

Many of these patients have no [symptoms], but those [who] do sometimes present with [swollen] lymph nodes. B symptoms aren't common. Occasionally patients can have night sweats or mild fatigue, but no true B symptoms. Our strategy with CLL to this day is still to watch and wait. In most patients who are asymptomatic, we wait for progressive disease. When I'm teaching students, I tell them [those are] the guidelines.

## The State of the Science

**O'BRIEN:** What is the mechanism of action of BTK inhibitors, and what is the rationale for using them in the treatment of CLL?

**BHAT:** To understand the mechanism of action of BTK inhibitors, we must understand the CLL cell. These cells accumulate in the body due to overproliferation and then forget to die due to a defect in a process called apoptosis. At the

center of this defect is the B-cell receptor [BCR], the BCR signaling pathway, which is known to play a very crucial role in the pathogenesis of many B-cell malignancies, including CLL.

BTK is a cytoplasmic tyrosine kinase, which is a critical step downstream in the BCR signaling pathway. Ibrutinib [Imbruvica] and other BTK inhibitors bind to the BTK at the C481 residue and block the tyrosine kinase activity, thereby preventing the pro-survival signals from traveling this pathway and blocking the proliferation of these cells.

**O'BRIEN:** How has ibrutinib performed in clinical trials?

**DANILOV:** The phase 3 RESONATE-2 trial [NCT01722487] led to the approval of ibrutinib in the frontline setting, and that's why ibrutinib was compared against chlorambucil [Leukeran], the old chemotherapy regimen used for the treatment of CLL.<sup>1,2</sup>

At the latest follow-up, ibrutinib was still associated with improved progression-free survival [PFS] and overall survival [OS] compared with chlorambucil. After 8-year follow-up, 42% of patients remain on ibrutinib and there were no new safety signals.

Of course, there's a risk of hypertension that doesn't go away with time, [as well as] atrial fibrillation, but many adverse effects [AEs] occur within the first 6 to 12 months and don't recur. Many patients do well on ibrutinib in the long term.

**O'BRIEN:** What are some of the differences between acalabrutinib [Calquence] and ibrutinib?

**COOMBS:** Acalabrutinib is a second-generation BTK inhibitor. The main differentiating feature is that it's more selective for BTK than ibrutinib. It produces fewer off-target events, which in theory leads to improved tolerability.

It has been studied in the frontline setting in the phase 3 Elevate-TN trial [NCT02475681].<sup>3</sup> I liked this trial because of its 3-arm design. The

standard arm examined chlorambucil and obinutuzumab [Gazyva], and there were 2 acalabrutinib-containing arms: one using acalabrutinib as a monotherapy and the other using it in combination with obinutuzumab. In addition to assessing the superiority of acalabrutinib vs chlorambucil with obinutuzumab, these data also give us a better sense of the efficacy of obinutuzumab, a newer anti-CD20 drug.

In Elevate-TN, acalabrutinib-treated patients had much better PFS as compared with chlorambucil-obinutuzumab. The prolonged follow-up showed some intriguing additional findings. The first is that those treated with acalabrutinib plus obinutuzumab seem to enjoy improved PFS, not only compared with the chlorambucil-obinutuzumab arm, but also compared with the acalabrutinib monotherapy arm. There are also some signals suggesting superior OS when comparing acalabrutinib plus obinutuzumab vs chlorambucil plus obinutuzumab.

Overall, this drug works well in the frontline setting, both as a monotherapy and in combination with obinutuzumab.

**O'BRIEN:** Could you comment on the different formulations of acalabrutinib?

**COOMBS:** The earlier capsule formulation of acalabrutinib faced one important barrier to its use: it could not be co-administered in the setting of a proton pump inhibitor [PPI]. Those are commonly used by classic elderly patients with CLL. PPIs could be used with H2 blockers, but it was a bit of a headache because you had to separate dosing by a couple of hours.

We now have results from the ELEVATE-PLUS study [NCT04768985; NCT04488016; NCT04564040], which examined a newer formulation of acalabrutinib as a tablet. These data show that this new formulation can be combined with PPIs, which is a huge advantage.<sup>4</sup> It allows the drug to be used in wider populations.

**O'BRIEN:** What were the findings of the phase 3 SEQUOIA trial [NCT03336333] examining zanubrutinib [Brukinsa]?<sup>5</sup>

**BHAT:** Zanubrutinib is another next-generation covalent BTK inhibitor, which is not currently approved for the treatment of CLL. SEQUOIA is an open-label, randomized, phase 3 study comparing continuous treatment with zanubrutinib vs chemoimmunotherapy plus bendamustine [Bendeka] and rituximab [Rituxan] as frontline therapy in elderly or unfit patients. Of note, patients with 17p deletion were excluded from the study.

SEQUOIA met its primary end point, showing superior PFS with zanubrutinib monotherapy vs bendamustine-rituximab, with a hazard ratio of 0.42. The zanubrutinib treatment was also better tolerated, and there was less myelosuppression with zanubrutinib. Other serious AEs also occurred less [often] in the zanubrutinib arm than in the bendamustine-rituximab arm.

These results were by no means a surprise; they were expected. They lent more support to the use of BTK inhibitors rather than chemoimmunotherapy in patients with CLL.

**O'BRIEN:** What data led to the approval of acalabrutinib as a relapse therapy?

**DANILOV:** The trial [that] led to the approval was the phase 3 ASCEND trial [NCT02970318].<sup>6,7</sup> ASCEND was unique because it was the first trial that compared a novel regimen with a novel regimen. Patients were randomly assigned to receive either acalabrutinib as a single agent or investigator's choice of idelalisib [Zydelig] plus rituximab or bendamustine plus rituximab. The trial met its primary end point: PFS at 4 years was around 60% in the acalabrutinib arm and around 20% in the control arm. Toxicities were manageable and mostly [consisted] of headaches, neutropenia, and diarrhea, mostly low grade. Most patients remained on the drug.

However, one needs to consider

how applicable this trial is to current practice. Many clinicians will know of patients who progressed on venetoclax [Venclexta], which is the type of patient who might receive a BTK inhibitor in the relapsed setting now that we use so much less chemoimmunotherapy. Nevertheless, ASCEND was an important study that solidified the role of acalabrutinib in the relapsed setting.

**COOMBS:** That study also demonstrates that overall response rate [ORR] isn't the best measure of success because all the arms had similar ORRs. Acalabrutinib works well [because] it's so much more tolerable and therefore has a much lower rate of discontinuation, which translates into that PFS benefit.

**O'BRIEN:** We also have a comparison of zanubrutinib to ibrutinib from the phase 3 ALPINE trial [NCT03734016].<sup>8</sup> ALPINE compared zanubrutinib with ibrutinib and their standard doses and showed that the response rate to zanubrutinib was higher than ibrutinib.

There has been some critique [of ALPINE] regarding the fact that a partial response with lymphocytosis was not included as a response. [However], when you do include a partial response with lymphocytosis, there's still a difference in favor of zanubrutinib, just not as large.

The question moving forward will be: how much should we extrapolate from the fact that ALPINE is in the relapsed setting? If clinicians consider a BTK inhibitor up front, they may choose [zanubrutinib] because they know in the relapsed setting it appeared more effective than ibrutinib.

### Selecting Between Treatments

**O'BRIEN:** How do you choose between BTK inhibitors?

**COOMBS:** It's a complicated question. I'm confident that the second-generation drugs—acalabrutinib and zanubrutinib—are safer based on the head-to-head data we have, though we don't have frontline data. The toxicities that occur

in the relapsed setting are likely similar to those that occur in the frontline setting.

My preference overall is to use the newer BTK inhibitors. My general practice has been to use acalabrutinib. However, there are scenarios in which I use zanubrutinib. For example, [I use it for] patients on a PPI. The newer formulation of acalabrutinib may [eliminate the need for this], though, since one can use acalabrutinib for patients on PPIs.

The other differentiating feature... is that zanubrutinib has lower toxicity rates in terms of atrial fibrillation, but it produces about the same rate of hypertension as acalabrutinib.

It's important to evaluate the patient's comorbidities and insurance [when selecting treatments]. They're both excellent drugs.

**DANILOV:** I mostly use acalabrutinib and zanubrutinib. Zanubrutinib has been added to the National Comprehensive Cancer Network compendium and I've obtained approval to use it for patients with CLL.<sup>9</sup>

Interestingly, in the ALPINE abstract, the ibrutinib treatment seemed to underperform. The 2-year PFS rate [achieved with] ibrutinib in that study was about 67.3% after a median of 1 prior therapy. In RESONATE-2, the 2-year PFS rate was nearly 80%, closer to the rate achieved with zanubrutinib in ALPINE. Discontinuation rates were also quite high in ALPINE—41% for ibrutinib and 26% for zanubrutinib. These are a little higher than what we're used to seeing in clinical trials of BTK inhibitors.

Nevertheless, this was a great result for zanubrutinib. I'm [excited for] longer follow-up and more data.

I'm on the fence regarding the choice between zanubrutinib and acalabrutinib. I don't use ibrutinib in my clinic anymore, though.

**BHAT:** Ibrutinib is associated with more toxicity both in the frontline and relapsed settings. The cardiac toxicity is especially important in our patients

with CLL, who are typically elderly and have cardiac comorbidities at baseline. I too have moved away from using ibrutinib [and instead favor] acalabrutinib and zanubrutinib.

How do we decide between them? We don't have enough data [yet]. Of course, it's easy to get acalabrutinib approved [for patients] because it's an FDA-approved agent. We've had instances in which patients experienced a particular AE on acalabrutinib and therefore had to switch to zanubrutinib, and vice versa. With the addition of the acalabrutinib maleate option, which counteracts the PPI limitation, acalabrutinib is a great choice for our patients.

**O'BRIEN:** How does real-world data play into your decision-making?

**DANILOV:** Large, multi-institutional data sets can teach us quite a lot. This is how we first learned about some of the complications of ibrutinib therapy, including cardiovascular complications, ventricular arrhythmias, and sudden death. We learned about high rates of ibrutinib discontinuation in real-world settings.

There were presentations at the 64th American Society of Hematology [ASH] Annual Meeting and Exposition assessing [the efficacy of] switching to acalabrutinib in patients who don't tolerate ibrutinib. There is some diversity in the data. In one large data set, for example, the authors showed that patients who switch from ibrutinib to acalabrutinib may not always enjoy a long time on acalabrutinib and may [often] switch to another class of agents.<sup>10</sup>

There was a phase 2 clinical trial in which patients who were intolerant of ibrutinib switched to acalabrutinib successfully. Most AEs did not recur over lower grade. There was a similar study in which patients took zanubrutinib if they were intolerant of ibrutinib or acalabrutinib.

Those trials may have a bit more weight than some of the real-world

analysis. However, real-world analysis can be hypothesis generating.

### Other BTK Inhibitors

**O'BRIEN:** What is pirtobrutinib and how is it used?

**COOMBS:** Pirtobrutinib is a noncovalent BTK inhibitor. The feature that distinguishes it from covalent inhibitors is that it doesn't require the presence of wild-type C481 to achieve optimal activity. Acquisition of mutations at that residue is the most common mechanism of resistance to covalent drugs as a class. The presence or absence of that mutation doesn't matter to pirtobrutinib, [and it] can still achieve effective binding given its distinct, reversible binding mechanism.

Pirtobrutinib has been extensively studied in CLL. The phase 1/2 BRUIN trial [NCT03740529] introduced it to the community.<sup>11</sup> This was a large study examining [this agent] in CLL and other B-cell malignancies. Pirtobrutinib treatment demonstrated very high ORRs and a meaningful PFS [improvement] of just under 20 months. This includes patients who are double exposed or double refractory, meaning they had experienced failed treatment with both a covalent BTK inhibitor and venetoclax. There's almost no effective off-the-shelf drug for this patient subgroup, but pirtobrutinib fortunately shows activity in this difficult-to-treat population.

**O'BRIEN:** Are there any other trials examining this agent?

**DANILOV:** There are a couple comparing pirtobrutinib against existing therapies. For example, the phase 3 BRUIN CLL-321 study [NCT04666038] will compare this agent against the investigator's choice of idelalisib-rituximab or bendamustine-rituximab. [Additionally], the phase 3 BRUIN-CLL-314 trial [NCT05254743] will compare pirtobrutinib against ibrutinib. Both trials are not yet mature; we don't have any data yet. Both trials assessed pirtobrutinib in earlier lines of therapy [and in]

double-refractory CLL. It will be interesting to see what transpires.

**O'BRIEN:** What is nemtabrutinib?

**BHAT:** Nemtabrutinib is another potent, noncovalent inhibitor of wild-type and C481-mutant BTK.

Bellwave-001 [NCT03162536] is a phase 1/2 study of the use of nemtabrutinib in a variety of hematological malignancies, including CLL. Previous data [have] shown this agent to be well tolerated, with manageable toxicities and a promising efficacy profile. Updated data regarding 57 patients with relapsed/refractory CLL were presented at this year's ASH Annual Meeting.<sup>12</sup> These patients were treated with 65 mg of nemtabrutinib, which was the recommended phase 2 dose. The [ORR] was roughly 56%. Most responses were partial, as is expected with BTK inhibitors.

Strikingly, for patients who had a response, the durability of response was just over 2 years, which is encouraging because this was a very refractory population. The median number of prior treatments was 4 [in this population]. Most of these patients had high-risk genomic features, including the BTK mutation, and 42% were dual refractory, meaning they had received both a BTK inhibitor and venetoclax in prior lines of therapy. The median PFS was 26.3 months, and the therapy was fairly well tolerated.

This is another agent we're looking forward to using in the treatment of relapsed/refractory patients.

**O'BRIEN:** What [are] the data on the use of venetoclax as continuous therapy?

**BHAT:** Venetoclax in clinical trial settings has been shown to be effective in all risk groups, including high-risk genomic groups. VerVe [NCT03342144] was a noninterventional, observational, real-world study of the use of venetoclax as a continuous monotherapy in patients with relapsed/refractory CLL who had both standard and high-risk genomic features, including 17p deletions [and]

*TP53* mutations, as well as [in] patients with *IGHV*-unmutated disease.<sup>13</sup>

Patients with *TP53* aberrations had the best [ORR]; it was around 74%, slightly lower than in patients with *TP53* wild-type disease. The estimated overall 1-year PFS for the whole group was around 80%. However, it was lower in patients with *TP53* aberrations. OS was also a little lower among these patients.

The study also showed that *IGHV* mutation testing is not typically conducted in the community. This testing should be standard for patients with CLL.

### Combination Regimens

**O'BRIEN:** What are the data regarding the combination regimen of ibrutinib and venetoclax?

**DANILOV:** An entire morning session of the ASH Annual Meeting was dedicated to doublets. There [were] a lot of exciting data.

[Data from] the phase 2 CAPTIVATE study [NCT02910583] were presented by John N. Allan, MD.<sup>14</sup> They focused on a cohort that achieved undetectable minimal residual disease [MRD] after induction with ibrutinib and venetoclax. Those patients were assigned to either receive placebo or ibrutinib.

Impressively, in both arms, most patients remained in undetectable MRD states. These MRD states were durable following finite-duration therapy with this doublet. The PFS rate after 4 years was roughly 95% in ibrutinib-treated patients and roughly 88% in placebo-treated patients. Of course, this is a small number of patients, and this was short follow-up.

It is still hard to say [which is better]; there is no statistical difference. Longer follow-up is needed to ascertain any differences.

Interestingly, patients assigned to receive ibrutinib tended to acquire more high-risk disease features, including more complex karyotypes and more *TP53*

aberrations. We will need longer follow-up to determine [whether] continuation of ibrutinib is necessary in these patients.

**O'BRIEN:** How should clinicians select between doublet and triplet therapies?

**BHAT:** The phase 2 CLL2-GIVE trial [NCT02758665] assessed the combination of ibrutinib, venetoclax, and obinutuzumab.<sup>15</sup> At the 2022 ASH Annual Meeting, data were presented on the triplet of venetoclax, acalabrutinib, and obinutuzumab.

In the phase 3 GAIA [CLL13; NCT02950051] study, both venetoclax plus obinutuzumab and venetoclax plus obinutuzumab plus ibrutinib were superior to chemoimmunotherapy [in terms of outcomes].<sup>16</sup> [However], we don't yet know what ibrutinib adds to the venetoclax-obinutuzumab doublet. Further data from this study should emerge in 2023.

In the United States, we have the phase 3 Alliance A041702 study [NCT03737981] and the phase 3 EA9161 study [NCT03701282] examining this triplet therapy. Until those data are available, it's too early to recommend triplet therapy, especially given the additional toxicity associated with adding an anti-CD20 monoclonal antibody to the doublet.

## Developments on the Horizon

**O'BRIEN:** What can we look forward to in this treatment landscape?

**COOMBS:** I'm extremely excited about the studies on combination regimens, and I'm also excited [to see data on] bispecific antibodies. I look forward to some presentations of that newer class of agents because they seem to be effective in the CLL and Richter transformation disease states.

**DANILOV:** There were a few takeaway lessons from this year's ASH Annual Meeting. The first is that we're just beginning to learn how and when to use doublet therapy. Hopefully, we'll know more in 3 or 4 years.

Secondly, noncovalent BTK inhibitors are an important immersion class of agents. I hope those will soon be approved.

We also need more targets. [Currently] we have BTK-targeting drugs, covalent and noncovalent, and BTK degraders, [all of which are] within the same pathway. [We also have] the BCL-2–targeting drugs, including venetoclax and others still in development. We need additional targets because double-refractory patients now present an unmet medical need.

**BHAT:** Over the [past] decade, targeted agents replaced chemoimmunotherapy [and] completely transformed the treatment of CLL. I [expect] further evolution in the use of these targeted agents [in the coming years], whether that happens through combination treatments or MRD-driven, time-limited therapies.

We will move further toward personalized treatment of patients with CLL. For example, there may be a patient for whom a continuous single-agent BTK inhibitor would be perfectly effective. [However], we might choose a combination regimen—a doublet or triplet—for another patient with an entirely different genomic profile and level of physical fitness.

Also, more targeted agents will join our toolbox in the relapsed/refractory setting. The future looks bright and interesting. ■

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