THE EXPANDING CONTINUUM OF CARE IN
Chronic Lymphocytic Leukemia

EVOLVING PARADIGMS

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Advances in the Bruton Tyrosine Kinase Inhibitor Class for CLL/SLL Treatment

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is an indolent B-cell lymphoma in which immature lymphocytes are found in the blood, bone marrow, and/or lymph nodes. Small lymphocytic lymphoma (SLL) is similar to CLL but has limited extension into the peripheral blood. CLL and SLL are considered different manifestations of the same disease and are therapeutically managed in the same way. The projected incidence of CLL in the United States is 21,250, with an estimated annual mortality of 4320.

The treatment landscape for CLL/SLL continues to rapidly evolve, and newer therapies have demonstrated improved survival and tolerability, particularly for patients within high-risk prognostic categories. Several small molecule immuno-oncologic agents (IOs) that target various mechanisms of B-cell differentiation and growth have been developed for use in CLL. These include anti-CD20 monoclonal antibodies (obinutuzumab, ofatumumab, and rituximab), PI3K inhibitors (idelalisib and duvelisib), a BCL2 inhibitor ([BCL2i] venetoclax), and Bruton tyrosine kinase (BTK) inhibitors ([BTKis]; ibrutinib and acalabrutinib) are FDA-approved for CLL/SLL, while zanubrutinib remains under clinical investigation in phase 3 trials.

BTK is an essential component of the B-cell receptor (BCR) signaling pathway required for proliferation, differentiation, development, trafficking, chemotaxis, adhesion, and cell survival. Autophosphorylation of BTK on the BCR activates its kinase activity, which subsequently sets in motion a cascade of downstream effects. The absence or inhibition of BTK has been correlated with a high rate of apoptosis in various B-cell lineages. Malignant B cells, as in the setting of CLL, upregulate BTK expression, making BTK an actionable therapeutic target to initiate malignant B-cell death.

Updated guideline recommendations set forth by NCCN in April 2021 recommend the use of a BTKi (ibrutinib monotherapy or acalabrutinib plus obintuzumab) for the first-line treatment of CLL/SLL. BTKi-based therapy is also among the recommended options for use in the second and subsequent treatment lines of CLL/SLL.

Studies examining the use of BTKi in the setting of CLL/SLL are abundant, yielding promising results. Among these are long-term safety and efficacy results for ibrutinib, efficacy trials of second-generation BTKis used as monotherapy, head-to-head trials comparing different BTKis, and trials examining use of BTKis in combination with other small molecule IOs or chemotherapy.

Drug Profiles

Ibrutinib

In 2014, ibrutinib became the first BTKi to be approved by the FDA. Ibrutinib
In CLL/SLL, treatment selection can be a complex process because of the variety of available therapies and combinations.

**Acalabrutinib**

The second-generation BTKI acalabrutinib, designed to limit inhibition of off-target kinases, was approved by the FDA in 2017 for mantle cell lymphoma (MCL) and received approval for the treatment of adult patients with CLL/SLL in 2019. It covalently binds to Cys481 in the active site of the ATP-binding domain of BTK. The standard dose is 420 mg orally once daily.

Among the BTKis, ibrutinib is the only FDA-approved agent that is indicated for the treatment of CLL/SLL with chromosome 17 deletion (del[17p]), a high-risk prognostic category. Ibrutinib remains the preferred single agent regimen for first-line CLL/SLL with del17p/TP53 mutation. Both acalabrutinib and ibrutinib are preferred agents for second-line adn subsequent therapy in patients with del(17p)/TP53 CLL/SLL.

In the pivotal RESONATE-2 (NCT01722487) study, an international, open-label, randomized phase 3 trial, investigators compared ibrutinib with chlorambucil in 269 treatment-naive patients 65 years of age or older with CLL. Ibrutinib showed superiority, with an estimated prolonged overall response rate (ORR) of 98% versus 85% with chlorambucil at 24 months (HR, 0.16; 95% CI, 0.05-0.56; \( P < .001 \)).

As a first-in-class therapy, ibrutinib has the longest follow-up data among BTKis, which demonstrate sustained efficacy and a consistent safety profile. In a 5-year efficacy and safety follow-up, the investigator-assessed ORR for ibrutinib was 92%.

AEs are the most common reason for ibrutinib discontinuation. In treatment-naive patients, the most common AEs leading to discontinuation were arthralgia (41.6%), atrial fibrillation (25.0%), and rash (16.7%); in patients with relapsed/refractory (R/R) disease, they were atrial fibrillation (12.3%), infection (10.7%), pneumonitis (9.9%), bleeding (9.0%), and diarrhea (6.6%).

**Zanubrutinib**

Zanubrutinib, a small molecule BTKi, is the newest member of the class, approved by the FDA in 2019 as a second-line therapy for patients with MCL. The standard dose is 320 mg orally once daily or 160 mg orally twice daily.

Phase 3 clinical trials to determine the efficacy and safety of zanubrutinib as a treatment for CLL/SLL are under way. In the ASCEND trial, 11% of patients discontinued zanubrutinib because of AEs, most of which were secondary primary malignancies followed by infection. The most common grade 3 or 4 AEs were neutropenia (16%; \( n = 24 \)), anemia (12%; \( n = 18 \)), and pneumonia (5%; \( n = 24 \)).

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**Clinical Developments**

**Head-to-Head BTKi Studies**

In CLL/SLL, treatment selection can be a complex process because of the variety of available therapies and combinations. Data from head-to-head comparison trials of BTKis may help physicians with choosing the appropriate agent for their patients.

Results from ELEVATE RR (NCT02477696), a phase 3, randomized, multicenter, open-label, noninferiority study of acalabrutinib versus ibrutinib in previously treated adult patients with high risk CLL/SLL (presence of del17p and/or del11q) are expected to be presented at a conference in 2021.

The primary end point was PFS after 36 months; secondary end points were incidence of AEs (≥ grade 3)...
infections, Richter transformation, and atrial fibrillation) and OS after 36 months. Inclusion criteria included presence of del(17p) and/or del(11q) as well as at least 1 prior therapy for CLL/SLL, not including a BTKi or BCL2i.19

Another study, ALPINE (NCT03734016), is an ongoing randomized, open-label, head-to-head phase 3 trial investigating the comparative efficacy and safety of zanubrutinib and ibrutinib monotherapy in 652 patients with R/R CLL/SLL.16,21 Patients are being randomized 1:1 to receive zanubrutinib 160 mg orally twice daily or ibrutinib 420 mg orally once daily.16 The primary efficacy outcome is ORR at up to 50 months.21 The estimated study completion date is August 1, 2022.21

**Combination Therapies**

Investigators are exploring novel combinations of BTKis with other agents (such as BCL2is and CD20is). A key focus on current combination therapy trials is whether BTKis in combination with other agents as part of time-limited regimens can lead to enduring remission as well as improved PFS and OS.

**Ibrutinib Combinations**

One promising combination is ibrutinib with venetoclax. Venetoclax causes CLL cell apoptosis; however, MCL1 proteins could protect CLL cells from mitochondria-mediated death.41 This could be prevented by ibrutinib-mediated BTK inhibition, which reduces MCL1 protein levels. Consequently, preliminary clinical trial results of this combination have shown complementary activities, synergistic interactions, and nonoverlapping toxicities.41

An investigator-initiated, open-label, phase 2 study from July 2016 through June 2018 examined the safety and efficacy of ibrutinib plus venetoclax in treatment-naive adult patients with CLL (N = 80).41 The primary end point was the best response (complete remission [CR] or complete remission with incomplete count recovery [CRi]) at any time during the treatment for up to 2 months after combined therapy completion.41 The median age was 65 years (range, 26-83), 30% of the patients were 70 years or older and 92% had unmutated IGHV, TP53 aberration, or del(11q). The median time to follow-up was 14.8 months.41

Patients received ibrutinib monotherapy (420 mg once daily) for 3 cycles, followed by the addition of venetoclax (weekly dose escalation to 400 mg once daily). Combined therapy was administered for 24 cycles.41 Eleven patients (14%) discontinued the study, 5 during the monotherapy phase and 6 during the combination phase.41

After 12 cycles of combined treatment, 88% of patients (29 of 33) reach CR or CRi and 61% (20 of 33) obtained undetectable minimal residual disease (uMRD).41 Responses were observed in all high-risk subgroups; in particular, (94%) of patients 65 years and older reached CR or CRi, and 76% reached uMRD by cycle 12.41

The combination’s toxicity and AE profile was similar to that of ibrutinib and venetoclax monotherapies; no new safety concerns were observed. Atrial fibrillation occurred in 15% of the patients. Grade 3 or 4 neutropenia, managed by granulocyte colony-stimulating factor support and dose interruptions or dose reductions of study drugs, was noted in 48% of patients. Neutropenic fever risk was 5%.41

The appropriate duration of ibrutinib plus venetoclax for CLL treatment is unclear and currently being investigated in trials such as CAPTIVATE (NCT02910583), a multicenter, 2-cohort, phase 2 study assessing both MRD-guided discontinuation and fixed-duration therapy for ibrutinib plus venetoclax in treatment-naive adult patients with CLL/SLL.42

The MRD-guided randomization phase of the MRD cohort examined whether this combination resulted in treatment-free remission in patients who reached uMRD. The primary end point was 1-year disease-free survival (DFS) among patients with confirmed uMRD.43 Among the 149 patients in this cohort, 58% obtained confirmed uMRD and were randomized to either continue ibrutinib alone (n = 43) or placebo (n = 43). The remaining 63 patients, who did not reach confirmed uMRD, were randomized to continue receiving ibrutinib (n = 31) or the combination (n = 32).43

Similar 1-year DFS was observed in patients with confirmed uMRD who continued treatment with ibrutinib (100%) or placebo (95.3%) and those without confirmed uMRD who continued treatment with ibrutinib (95.2%) or ibrutinib with venetoclax (96.7%).41

Most AEs were grade 1 or 2 and occurred most frequently in early cycles of the combination arm. The most common grade 3 or 4 AEs were neutropenia (36%), hypertension (10%), thrombocytopenia (5%), and diarrhea (5%). No new safety concerns were observed.43

**Acalabrutinib Combinations**

As a highly selective, covalent inhibitor of BTK with minimal off-target activity, acalabrutinib does not inhibit IL-2–associated tyrosine kinase; thus, interference with antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity is minimal. This may allow for effective combination with obinutuzumab.29

ELEVATE CLL TN (NCT02475681), a global, phase 3, multicenter, open-label study in adult patients with treatment-naive CLL, compared the efficacy of acalabrutinib with or without obinutuzumab against chlorambucil with obinutuzumab. The primary end point was PFS.28 Eligible patients were adults 65 years and older with multiple comorbidities (N = 535); they were randomized 1:1:1 to each study group.28

Estimated PFS at 24 months was 93% with acalabrutinib-obinutuzumab (95% CI, 87%-96%), 87% with acalabrutinib-
monotherapy (95% CI, 81%-92%), and 47% with obinutuzumab-chlorambucil (95% CI, 39%-55%). The HR for PFS between acalabrutinib-obinutuzumab and acalabrutinib monotherapy was 0.49 (95% CI, 0.26-0.95).

The most common grade 3 or higher AE across groups was neutropenia (30% in the acalabrutinib-obinutuzumab group, 10% in the acalabrutinib group, and 41% in the obinutuzumab-chlorambucil group). Grade 3 or higher infections occurred in 21% of patients given acalabrutinib-obinutuzumab, 14% of patients given acalabrutinib monotherapy, and 8% of patients given obinutuzumab-chlorambucil. Deaths occurred in 5% of patients given acalabrutinib-obinutuzumab, 7% of patients given acalabrutinib, and 9% of patients given obinutuzumab-chlorambucil.

**Zanubrutinib Combinations**

Zanubrutinib, obinutuzumab, and venetoclax in combination are being studied as a therapy for adult patients with treatment-naive CLL/SLL in NCT03824483, a multicenter, investigator-initiated, phase 2 trial. The primary outcome measure is rate of uMRD after 1 year. Treatment was administered in 28-day cycles for a minimum of 8 cycles. Patients (N = 37) received zanubrutinib (160 mg) orally twice daily starting on day 1 as well as obinutuzumab (1000 mg IV) on days 1, 2, 8, and 15 of cycle 1 and day 1 only of cycles 2 through 8. Venetoclax once daily was added to the regimen on day 1 of cycle 3. MRD was assessed in peripheral blood (PB) starting on day of cycle 7 and again every 2 cycles. Once peripheral marrow uMRD was confirmed in bone marrow (BM), treatment continued an additional 2 cycles.

Initial results showed that PB MRD of less than 0.1% was obtained in about 22% of patients; about 68% of patients obtained PB uMRD. Among the patients with PB uMRD, 76% had BM uMRD; of these, about 53% discontinued after 2 more cycles of treatment. BM MRD was found in 12% of patients (n = 3) with PB uMRD. At the time the study was published, BM uMRD confirmation was pending for 12% of patients with PB uMRD.

Grade 3 or higher AEs occurring in at least 5% of patients included neutropenia (13%), thrombocytopenia (5%), rash (5%), and pneumonia (5%).

**Future Directions**

A BTKi with chemotherapy regimen may be a potent and time-limited regimen for younger, fit patients with CLL. NCT02251548, a phase 2, multicenter, open-label, non-randomized, single-arm phase 2 trial of adult patients 65 years or younger with previously untreated CLL (N = 85), evaluated the proportion of patients who achieved CR with BM uMRD for 2 months after the last cycle of ibrutinib plus fludarabine, cyclophosphamide, and rituximab.

Results from the study found that 71 patients (84%) obtained BM uMRD. One patient died of a presumed cardiac event after 17 months of ibrutinib maintenance. The most common all-grade AEs included thrombocytopenia (74%), neutropenia (62%), and anemia (49%). Grade 3 or 4 nonhematological serious AEs included grade 3 atrial fibrillation in 3 patients (4%), and grade 3 Pneumocystis jirovecii pneumonia in 2 patients (2%).

**Addressing Treatment Resistance**

Long-term efficacy of BTKis can be limited by the development of resistance, which is often due to BTK cysteine-481 (C481S) mutations. As stated by Mato et al, “covalent BTK inhibitors also have low oral bioavailability, short half-lives, and high protein binding, resulting in brief periods of exposure required to bind and inactivate BTK.” Among the experimental BTKis under investigation to address this problem is pirtobrutinib (previously LOXO-305), an oral, reversible, noncovalent inhibitor for both wild-type and C481 BTK.

The phase 1/2, first-in-human, open-label BRUIN study (NCT03740529) evaluated the safety and efficacy of pirtobrutinib in patients with previously treated B-cell malignancies, including those with CLL/SLL. Of the 121 efficacy evaluable patients with CLL/SLL treated with 200 mg pirobrutinib daily, the ORR was 62%. ORR was similar among patients with CLL/SLL with previously treated B-cell malignancies, including those with CLL/SLL. Of the 121 efficacy evaluable patients with CLL/SLL treated with 200 mg pirobrutinib daily, the ORR was 62%. ORR was similar among patients with CLL/SLL with previous covalent BTKi resistance (67%), covalent BTKi intolerance (52%), BTK C481-mutant (71%), and BTK wild-type disease (66%).

Dose-limiting toxicities were observed and the maximally tolerated dose was not reached. Among all patients included in the BRUIN study (N = 323), the most common grade 3 or higher AE was neutropenia (10%). Any grade

A BTKi with chemotherapy regimen may be a potent and time-limited regimen for younger, physically fit patients with CLL.
AEs occurring in at least 10% of patients were fatigue (20%), diarrhea (17%), and contusion (14%).\(^{48}\)

ORR with pirtobrutinib was 62% among 121 efficacy evaluable patients with CLL/SLL.\(^{48}\) ORR was similar in patients with CLL with previous covalent BTKi resistance (53 of 79; 67%), covalent BTKi intolerance (22 of 42; 52%), BTK C481-mutant (17 of 24; 71%), and BTK wild-type disease (43 of 65; 66%).\(^{48}\)

Longer follow-up is needed to determine the response durability and safety profile of pirtobrutinib, but this and other third-generation prospective BTKis may address the growing unmet needs of patients who require alternate therapies.\(^{48}\)

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Q&A WITH JENNIFER A. WOYACH, MD

Seeing the Bigger Picture: Expert Perspective on the Changing BTK Inhibitor Landscape

Ibrutinib is the benchmark by which we judge newer BTK inhibitors.”
—JENNIFER A. WOYACH, MD

Targeted Oncology (TO): Could you reflect on the Bruton tyrosine kinase (BTK) inhibitor class and its trajectory within the CLL treatment landscape, specifically what makes this class different from other targeted therapies?

WOYACH: BTK inhibitors have changed the treatment paradigm in CLL. They are the first targeted therapies to show a big improvement in progression-free survival compared with standard chemotherapy or chemoimmunotherapy. This class has really changed the approach to treating CLL, where the disease is now, for many patients, treated more like a chronic disease, similar to diabetes or hypertension. Patients can take a pill daily or twice a day for, hopefully, many years. Moving forward, we will continue to see BTK inhibitors used in this way in many patients. Now that we have many more targeted agents and an increased understanding of disease biology, we have the opportunity to create strategic combinations of therapies with the goals of getting patients off therapy. We also continue to work toward eliminating the disease entirely for many patients.

TO: As the treatment spectrum expands, how has ibrutinib’s role changed as the BTK inhibitor spectrum has evolved, and what is the significance of having longer-term data regarding overall survival and duration of response?

WOYACH: Ibrutinib is the benchmark by which we judge newer BTK inhibitors. Certainly, it will always have the longest follow-up and probably will always have the most robust data in terms of the number of patients treated on single-agent studies through which to evaluate long-term side effects. Compared with some of the second-generation BTK inhibitors, there are advantages to ibrutinib in some patients, including the once-daily dosing and limited drug interactions. There is also a lot of familiarity with ibrutinib because clinicians have been using it for quite a few years.

Right now, having this extensive body of long-term data is important because we are still identifying side effects and patterns of response and relapse. Especially with a drug that patients might take for many years, it is important to have robust long-term data to be aware of if any side effects arise with long-term treatment.
TO: How would you assess the relevance of recent analyses evaluating ibrutinib in patients with TP53 alterations, and what would you like to see emphasized in future research when it comes to evaluating the potential of BTK inhibitors in higher-risk subpopulations?

WOYACH: The pooled analysis from TP53-altered patients [presented at the American Society for Hematology 2020 Annual Meeting] was really helpful, especially in the front-line setting, because it showed that ibrutinib, and potentially this class of BTK inhibitors, can overcome the negative prognostic value of a TP53 abnormality, at least in the short to intermediate term.

There are a lot of data available with novel agents in the treatment of patients with TP53-altered CLL because this is a relatively large group in the setting of relapsed disease. Many other genetic abnormalities in CLL are seen much less commonly, so it is only in large studies that we can begin to explore trends. Every bit of information we can collect is important, though, so that we can truly personalize care for patients.

TO: What are some of the most notable learnings regarding safety you’ve taken away from continued investigation into ibrutinib and the BTK class more generally, specifically when it comes to toxicity profile with these agents?

WOYACH: With ibrutinib, as a result of having extended follow-up on many patients, the safety profile is really well articulated and established. We know that there are common toxicities that sometimes cause patients to discontinue therapy but are more QOL [quality-of-life] altering rather than specifically dangerous; these include arthralgias, gastrointestinal symptoms, and fatigue. Then we have toxicities that are much less common but more dangerous, such as atrial fibrillation, ventricular arrhythmias, hypertension, and bleeding. The cardiac toxicities appear to not be entirely dependent on BTK because they are more common with ibrutinib than with the more selective second-generation inhibitors.

TO: How would you assess the relevance of recent analyses evaluating ibrutinib in patients with TP53 alterations, and what would you like to see emphasized in future research when it comes to evaluating the potential of BTK inhibitors in higher-risk subpopulations?

WOYACH: This is where the current head-to-head trials of novel agents are so critical. We have multiple drugs approved in the frontline setting, with all the approvals based upon randomized studies with chemoinmunotherapy. Although the efficacy of all the approved BTK inhibitors, as well as venetoclax/obinutuzumab, appears similar given the available follow-up, cross-trial comparisons are notoriously unreliable. Although these head-to-head studies take a long time to complete, they are invaluable for differentiating these agents in terms of safety and efficacy, to really help to identify the best treatment for an individual patient.

Right now, prior to therapy, it is important to know IGHV mutation status, TP53 mutation status, and del(17p) status, as well as the patient’s medical history, concomitant medications, and current symptoms. The disease-related factors can help narrow down therapies; for example, I would only consider chemotherapy for an IGHV-mutated patient; for a patient with TP53 abnormalities, I generally will use a BTK inhibitor. But in the absence of head-to-head trials showing that one drug is superior to another, a lot of the decision comes down to discussing different therapies with the patient and shared decision-making around indefinite vs fixed-duration therapy and choosing a drug based upon known side effects.

TO: As the BTK inhibitor landscape and the broader CLL treatment spectrum continue to expand, what factors should clinicians consider when selecting a treatment?

WOYACH: The biggest question right now is whether BTK inhibitors are best administered alone or in combination with other agents such as venetoclax. There are studies that are designed to answer that question, but it’s going to take a long time to get those results because these drugs work so well. However, this is something that is going to be very important to tease out because it has many implications on toxicity, especially chronic toxicity, as well as financial implications because a combination comes with an up-front increase in cost but may be more economical in the long term if a long, treatment-free interval can be experienced. TT

In the absence of head-to-head trials showing that one drug is superior to another, a lot of the decision comes down to discussing different therapies with the patient and sharing decision-making around indefinite vs fixed-duration therapy and choosing a drug based upon knowing the side effects.”

—JENNIFER A. WOYACH, MD
Clinical Considerations for Combination Therapies in Patients With Treatment-Naive or Relapsed/Refractory CLL/SLL

**Targeted Oncology (TO):** What factors do you consider when deciding treatment regimens for adult patients with chronic lymphocytic/small lymphocytic lymphoma (CLL/SLL)?

**PHILIP THOMPSON:** If we’re talking about frontline CLL, the first question I always consider is: “Is this a patient where I would consider chemoimmunotherapy?” That’s a very narrow group of patients who are young and fit and have favorable genomic features. Every patient should have a genomic evaluation before they start treatment, which includes \( IGHV \) somatic hypermutation analysis, FISH [fluorescence in situ hybridization] looking for a chromosome 17p deletion, and next-generation sequencing looking for \( TP53 \) mutations. If a patient doesn’t have \( TP53 \) abnormalities, doesn’t have 11q deletion, and has a mutated \( IGHV \), then they’re a potential candidate for chemoimmunotherapy, although I’ll tell you that there aren’t too many patients who are particularly excited about receiving chemoimmunotherapy. I rarely prescribe it now. But for that favorable prognostic group of patients, there are very encouraging data from CLL14 with venetoclax and obinutuzumab, and those patients have a very high rate of achieving undetectable minimal residual disease [MRD] after therapy.

In that group with a mutated \( IGHV \), I think the favorable results you get with time-limited chemoimmunotherapy are probably also going to be seen with time-limited treatment with venetoclax [and] obinutuzumab in that group. Those patients who have a \( IGHV \) mutation, I prescribe it now. For for that favorable prognostic group of patients, there are very encouraging data from CLL14 with venetoclax and obinutuzumab, and those patients have a very high rate of achieving undetectable minimal residual disease [MRD] after therapy.

**TO:** Do the considerations differ for relapsed and refractory?

**PHILIP THOMPSON:** They do. I mean the data are a little bit different. There are no data for BTK [Bruton tyrosine kinase] inhibition plus obinutuzumab in relapsed patients. There are data for ibrutinib/rituximab compared with ibrutinib monotherapy from [the University of Texas] MD Anderson [Cancer Center], which were negative; they showed no difference between the ibrutinib/rituximab versus ibrutinib monotherapy arm.

**TO:** There are trials under way that are investigating BTK inhibitors in combination with other agents, such as ibrutinib with venetoclax and acalabrutinib with obinutuzumab. What’s your expectation for these combination therapies?

**PHILIP THOMPSON:** There’s a dizzying array of studies going on; basically, they’re testing all...
permutations, doublets with a BTK inhibitor, and a BTK inhibitor plus venetoclax, plus or minus CD20 antibodies. I think it’s going to be really interesting.

It’s not going to be surprising to know that if you use a BTK inhibitor plus venetoclax, you’re going to do much better than with chemoimmunotherapy. There will be a higher rate of undetectable minimal residual disease. Patients with high-risk genetics will do much better with targeted agents.

What I think we don’t know here is, when you use ibrutinib plus venetoclax or acalabrutinib plus venetoclax, do you need a CD20 antibody on top of that? My suspicion is that a CD20 antibody is going to add very little to that combination. I don’t know for sure, but when you look at some of the triplet regimens from phase 2 studies, the undetectable MRD rates seem fairly similar to what you get with just ibrutinib/venetoclax or acalabrutinib/venetoclax. But there are ongoing randomized studies that are going to properly answer that question. There are some that are going to directly compare BTK monotherapy versus BTK inhibitor plus venetoclax.

**TO:** For BTKi combination therapies, what would you like to see in clinical trials to determine the number of cycles and length of maintenance therapy?

**THOMPSON:** There were several phase 2 studies—one at MD Anderson and one in the UK with ibrutinib and venetoclax—where there was an MRD-directed approach to treatment duration. In the CAPTIVATE trial, patients get ibrutinib for 3 cycles, then ibrutinib plus venetoclax for 12 cycles. Twelve months, 48 weeks of combination therapy. If they have undetectable MRD and are confirmed undetectable MRD, they get randomized to ibrutinib maintenance versus no maintenance at that point. If they have detectable MRD, they get randomized to discontinuing ibrutinib monotherapy or continuing combination therapy with ibrutinib and venetoclax.

That’s an attempt to try to use MRD analysis to guide duration of therapy. The UK study uses a similar approach where basically they treat to undetectable MRD targets. If patients do not achieve early undetectable MRD, they continue the combination therapy with ibrutinib/venetoclax or venetoclax for longer. If they still have MRD at the end of 3 years, they continue ibrutinib monotherapy. My colleague Dr [Nitin] Jain [, MD, the University of Texas MD Anderson Cancer Center, Houston, TX] had a similar study to that in both frontline and relapsed patients where they were treated for 2 years; if they had MRD at the end of treatment, they continued ibrutinib maintenance, and if they had undetectable MRD, they stopped. This is an example of an MRD-directed approach, which I think some people are going to do as part of their routine practice.

**TO:** Looking specifically at ibrutinib/venetoclax, what is your perspective regarding the implications and potential benefits of 2 oral oncolytics coming together?

**THOMPSON:** Each drug makes the other drug work better. They target completely different pathways in the cell so that should—theoretically and in practice—dramatically reduce the risk of resistance emergence during therapy, particularly at point mutations in BTK or BCL2 emerging during therapy. We’ve seen very few patients develop on-treatment resistance in our ibrutinib/venetoclax studies. The drugs have nonoverlapping toxicity profiles, which is hugely useful. Really, the only [adverse] effect that we see is that worse with combination than with either drug alone is diarrhea. There’s more diarrhea on that combination than with either drug alone because both of those 2 drugs can cause usually relatively minor diarrhea. Most patients are able to tolerate that combination very well.

**TO:** There are a few studies under way evaluating BTKis with chemoimmunotherapy for treatment-naive CLL/SLL. Are there any data that you find compelling, and how could this affect treatment?

**THOMPSON:** Yes, there are 3 studies in particular. There’s one led by Dr Matthew S. Davids [, MD, MMSC] at Dana-Farber [Cancer Institute, Boston, MA] with ibrutinib and FCR. That study included all patients, regardless of genomic risk, so they had patients with 17p deletion, for example, on that study. And they had an extremely high response rate and rate of undetectable minimal residual disease, I think around 80% with undetectable MRD on that study. And a very high rate of progression-free survival. So overall, it was an extremely potent regimen. It’s a time-limited regimen. They didn’t select patients according to genomics.

But the challenge is, you’re still giving chemoimmunotherapy. You’re still exposing the patient to the risks associated with chemoimmunotherapy; in particular, the risk of secondary myeloid neoplasms like MDS [myelodysplastic syndromes] and AML [acute myeloid leukemia], which occur in 2% to 5% of patients who receive FCR. And it’s a devastating, usually fatal, complication. So, most people, I think, are leaning away from chemoimmunotherapy for that reason, given that we can get such high rates of undetectable MRD with venetoclax-based therapy.

If you’re hoping to achieve undetectable MRD with time-limited treatment, most people are going to say, “Well, OK, I’ll use a venetoclax-based treatment rather than adding a BTK inhibitor to chemotherapy.” I think that’s probably the way the field is headed. It’s hard for me to see a path forward to widespread use of chemoimmunotherapy plus a BTK inhibitor. **TT**