

OncLive[®]

CHRONIC LYMPHOCYTIC LEUKEMIA

APRIL 6, 2022

VIRTUAL WORKSHOP

SCIENTIFIC **INTERCHANGE & WORKSHOP**

New Directions in **Chronic
Lymphocytic Leukemia**

The background of the lower half of the image is a dark blue, textured surface resembling a microscopic view of cells or a molecular structure. Overlaid on this are several white geometric patterns: solid circles, dashed circles, and intersecting lines. Small white plus signs are scattered across the scene, some appearing to be on the textured surface and others floating in the space.

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CLL



KEY TAKEAWAYS

- ▶ Due to lower rates of adverse events that include atrial fibrillation, bleeding, and hypertension, next-generation Bruton tyrosine kinase inhibitors (BTKis), such as acalabrutinib and zanubrutinib, are becoming favored treatment options in place of ibrutinib.
- ▶ Noncovalent, reversible BTKis, such as pirtobrutinib, have demonstrated potency for both wild-type and C481-mutated BTK variants and may offer new strategies in overcoming BTKi resistance.
- ▶ With demonstrated efficacy for mono- and combination therapy approaches as well as durable responses in patients with chronic lymphocytic leukemia (CLL) and deletions in the short arm of chromosome 17 (del[17p])/TP53 mutations, venetoclax offers expanded therapeutic options for patients with high-risk disease as well as fit, younger patients who may benefit from a more intensive treatment approach.
- ▶ Impacts of coronavirus disease 2019 (COVID-19) to the CLL treatment landscape include the emergence of tixagevimab-cilgavimab as a treatment option for COVID-19 pre-exposure prophylaxis and an overall increased hesitancy among providers regarding the use of anti-CD20 antibodies for combination therapeutic strategies.
- ▶ High-risk patients, such as those with del(17p)/TP53 mutations, NOTCH1 mutations, or complex karyotype may receive greater benefit with continuous vs fixed-duration therapy.

New Directions in Chronic Lymphocytic Leukemia

INTRODUCTION

On April 6, 2022, the *OncLive®* Scientific Interchange: New Directions in Chronic Lymphocytic Leukemia (CLL) featured a panel of oncology experts who specialize in the treatment of hematological malignancies. Benjamin Heyman, MD, assistant clinical professor of medicine at University of California San Diego Health in La Jolla, CA, served as the moderator. The goals of the interchange were to discuss the treatment landscape and evaluate therapeutic strategies employed in treating patients with CLL; obtain feedback on relevant patient considerations and other factors that affect treatment selection;

and gain insight into how novel regimens, combination therapies, and ongoing clinical trials may impact the treatment landscape.

CURRENT STANDARD OF CARE IN CLL

Before the introduction of novel, targeted therapies, the standard-of-care treatment of CLL involved the use of chemoimmunotherapy (CIT) regimens, such as fludarabine plus cyclophosphamide and rituximab, bendamustine plus rituximab, or chlorambucil with or without rituximab.¹ However, with increased understanding of disease biology, an expansion of therapeutic options has ensued, along with a subsequent transformation in the treatment approach for patients with CLL.² Although CIT remains a viable option for some patients, novel targeted therapies, including inhibitors of Bruton tyrosine kinase (BTK), B-cell lymphoma 2 (BCL2), and phosphatidylinositol 3-kinase (PI3K), have largely replaced conventional CIT-based strategies; these agents offer notable single-drug efficacy and chemotherapy-free treatment options.^{3,4}

FRONTLINE TREATMENT OF CLL

Ibrutinib, a first-generation, irreversible covalent BTK inhibitor (BTKi), is widely regarded as the first drug in the evolution of CLL treatment strategies.^{2,5,6} Efficacy data supporting the use of ibrutinib were initially established by the RESONATE-2 study (NCT01722487), a phase 3 trial evaluating ibrutinib vs chlorambucil.^{7,8} With 8 years of follow-up safety and efficacy data, ibrutinib is now established as a recommended first-line therapy option for CLL.^{5,6} However, toxicities such as bleeding, atrial fibrillation, and hypertension can lead to treatment discontinuations and dose interruptions that may limit efficacy and shorten event-free survival in some patients, including those receiving continuous therapy.^{2,3} This consequently led to the development

of next-generation BTKis with greater selectivity and improved tolerability.^{2,3} With demonstrated efficacy in patients with deletion in the short arm of chromosome 17 (del[17p])/TP53 mutations, the BCL2 antagonist venetoclax has emerged as another important first-line agent that offers expanded treatment options for patients ineligible for BTKi monotherapy.^{3,9,10} Important considerations that can guide treatment selection and sequencing strategies include patient preferences, disease status, comorbidities, and safety profiles associated with potential treatments.³

STAKEHOLDER INSIGHTS

First-Line Treatment Strategies for CLL

Faculty members agreed that patient preference plays a large role in the first-line treatment strategy, with 1 participant highlighting the importance of patient discussions regarding differences between treatments, such as the duration of therapy, mild or ongoing adverse events (AEs) that may occur with BTKis, and the rigors of monitoring associated with venetoclax and obinutuzumab combination therapy. Other panelists noted that factors such as concomitant proton pump-inhibitor (PPI) therapy in BTKi-eligible patients, renal function with anti-CD20 monoclonal antibodies, and the risk of infusion reactions with obinutuzumab in frail patients may also affect treatment selection.

In terms of BTKi eligibility and selection, the panel highlighted that, in patients with significant cardiac risk, there is a concern about cardiac complications that have been observed in BTKi therapy. Because this is more commonly associated with first-generation BTKis, a

second-generation BTKi may be preferred in this clinical scenario. Faculty members acknowledged that for patients receiving dual antiplatelet therapy or those with a bleeding disorder, a venetoclax-based therapy may be preferred over a BTKi-based regimen, and certain BTKis should be avoided in patients who require long-term PPI treatment.

Fixed-Duration vs Continuous Therapy Regimens

General consensus among panel members was that high-risk patients, such as those with del(17p)/TP53 mutations, NOTCH1 mutations, or complex karyotype often respond better to continuous vs fixed-duration therapy. In further discussion, 1 participant underscored that venetoclax plus obinutuzumab may be an option for young patients with chromosome 17 mutations who don't want continuous therapy.

Impact of COVID-19 on Treatment Strategies

Panelists discussed how the coronavirus disease 2019 (COVID-19) pandemic influenced treatment selection for their patients with CLL. Overall, panelists have been hesitant to use anti-CD20-directed agents, both as a monotherapy and in combination with BTKis due to cases of post-COVID-19 pneumonitis. While anti-CD20 agents are considered for use as fixed-duration therapies in some cases, overall, panelists indicated there are limited benefits with the addition of anti-CD20 agents to a BTKi for initial CLL treatment in some patients. The development of Richter syndrome and mutations that can occur during the watch-and-wait period were raised as areas

of concern and reasons that anti-CD20 agents are avoided. Early case reports suggesting that BTKis may play a role in lessening the cytokine storm associated with COVID-19 infections were discussed. The combination of tixagevimab and cilgavimab is available for use in the prevention of COVID-19 infection before known exposure for use in certain populations, including those with CLL who are moderately to severely immunocompromised and receiving immune-suppressing treatment (eg, BTK inhibitors, CD20 antibodies, etc). Panel members agreed that much remains unknown regarding how the virus may mutate and if pre-exposure prophylaxis will continue to be an effective strategy in the future.

RELAPSED/REFRACTORY CLL

Despite advancements in the therapeutic landscape for CLL, some patients are refractory to or intolerant of available therapies, and many patients eventually experience relapse, highlighting the need for expanded treatment options.¹¹ When compared with ibrutinib, next-generation BTKis such as acalabrutinib and zanubrutinib have demonstrated lower rates of AEs, including atrial fibrillation, bleeding, and hypertension, and offer an alternative treatment option for patients who are intolerant to ibrutinib or may not be ideal candidates for continuous ibrutinib.^{8,12,13} Other novel treatment approaches being investigated in the relapsed or refractory treatment setting include noncovalent BTKis, bispecific antibodies, and chimeric antigen receptor (CAR) T-cell therapies.³

STAKEHOLDER INSIGHTS

Approach to Treatment Selection in Relapsed or Refractory CLL
Panelists indicated that the treatment approach for relapsed

or refractory CLL can be similar in some ways to the first-line setting, where BTK and BCL2 inhibition are considered equivalent options. One participant pointed out that for patients who progress on BTKi therapy, the next best choice (based on available data) is to follow with BCL2 inhibition. The faculty noted that data on BTKi therapy following progression on a BCL2 inhibitor is limited, although the MURANO study (NCT02005471) suggests that there may be benefit.¹⁴ In terms of treatment sequencing, faculty emphasized the importance of maximizing the benefit from 1 treatment before moving on to other lines of therapy and added that retreatment with venetoclax may be considered if the patient has had a treatment-free interval period of approximately 2 years.

Regarding BTKi selection in a relapsed setting, the general consensus among panelists was that agents in this class appear to be equally efficacious but have very different AE profiles. Overall, the second-generation BTKis acalabrutinib and zanubrutinib are preferred over ibrutinib due to improved tolerability, although some of the faculty appeared to have preference for 1 versus the other in certain clinical scenarios.

The Role of PI3K Inhibitors in Refractory or Relapsed CLL

PI3K inhibitors were identified as an appropriate treatment option in the third-line setting, for patients with BTKi intolerance, and for patients who are ineligible for venetoclax-based regimens. For patients who are refractory to BTKis, treatment with a single-agent PI3K inhibitor is unlikely to produce a strong and long-term response. As PI3K inhibitors are tolerated with short-term treatment,

panelists identified that they may have a useful role as a bridging therapy. Intermittent dosing with a PI3K inhibitor may also provide an option for patients who temporarily hold treatment due to AEs. The faculty acknowledged that the newer-generation PI3K inhibitors are an improvement from the first-generation compounds.

THE POTENTIAL IMPACT OF ZANUBRUTINIB ON THE TREATMENT LANDSCAPE

Off-target activity related to HER2, HER4, TEC, and other kinase receptors are believed to be associated with treatment-emergent AEs (eg, rash, diarrhea, bleeding, infections, and atrial fibrillation) observed with BTKis.¹³ Next-generation BTKis such as acalabrutinib and zanubrutinib have been shown to have greater selectivity for BTK with fewer off-target effects and lower rates of atrial fibrillation, bleeding, and hypertension.^{15,16} Zanubrutinib was granted accelerated approval from the United States Food and Drug Administration (FDA) on September 14, 2021, for use in patients with relapsed or refractory marginal zone lymphoma (MZL), and it has shown promising results in ongoing trials investigating use in patients with previously untreated and relapsed or refractory CLL.¹⁷⁻²¹

THE ALPINE TRIAL Study Design

The ongoing randomized, open-label ALPINE trial (NCT03734016) is a phase 3 study evaluating the efficacy of zanubrutinib vs ibrutinib in patients with relapsed or refractory CLL or small lymphocytic leukemia (SLL).²² The trial includes approximately 400 patients stratified by age, refractory status, geographic region, and presence of del(17p)/TP53 mutation. Patients who received prior treatment with a BTKi or who had a current or past history of Richter syndrome, history of

severe bleeding disorder, or clinically significant cardiovascular disease were excluded from the study.²² Patients were randomly assigned 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg daily until disease progression.²²

Baseline demographic and disease characteristics of patients in both the zanubrutinib and ibrutinib treatment arms were balanced. The treatment arms had a comparable proportion of patients aged 65 years and older (62.3% vs 61.5%), and the arms had a similar percentage of men (68.6% vs 75.0%). Balance was seen in the proportion of patients who had received at least 3 prior lines of therapy (7.2% vs 10.1%) as well as those with the presence of del(17p) (11.6% vs 12.5%) and TP53 mutations without del(17p) (8.2% vs 5.8%).²⁰

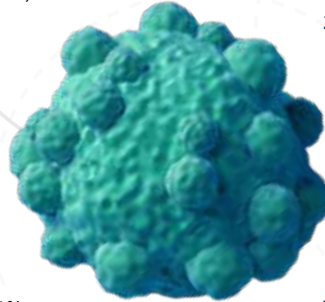
The primary end point for the study was overall response rate (ORR) determined by an independent review committee (IRC) per International Workshop on CLL (iwCLL) guidelines for patients with CLL (which included modifications made for treatment-related lymphocytosis for patients with CLL) and according to the 2014 Lugano classification for patients with SLL.²² Key secondary end points included progression-free survival (PFS), duration of response (DOR), overall survival (OS), safety, and patient-reported outcomes.²² Additionally, the correlation between clinical outcomes and prognostic and predictive biomarkers were exploratory end points for the study.²²

Results

Upon a median follow-up of 15 months, reported ORR was significantly higher in the zanubrutinib vs ibrutinib group (78.3% vs 62.5%; $P = .0006$).²⁰ ORR was higher in the zanubrutinib arm than the ibrutinib arm for patients with a deletion in the long arm of chromosome 11 (del[11q]) (83.6% vs 69.1%) and for those with del(17p) (83.3% vs 53.8%). The 12-month PFS was significantly

higher for patients who received treatment with zanubrutinib (94.9%) vs those who received ibrutinib (84.0%) with an associated hazard ratio of 0.40 (95% CI, 0.23-0.69; $P = .0007$). OS was also higher in the zanubrutinib arm (97.0%) compared with the ibrutinib arm (92.7%).²⁰

The occurrence of atrial fibrillation or flutter was significantly lower in the zanubrutinib vs ibrutinib arm (2.5% vs 10.1%; $P = .0014$).²⁰ Patients receiving zanubrutinib also experienced lower rates of major bleeding (2.9% vs 3.9%), AEs leading to treatment discontinuation (7.8% vs 13.0%), and death (3.9% vs 5.8%).²⁰ Although the rate of neutropenia was higher among patients receiving zanubrutinib vs those given ibrutinib (28.4% vs 21.7%), the number of reported infections of grade 3 or higher were lower in the zanubrutinib arm (12.7% vs 17.9%).²⁰



its use may be preferred over ibrutinib in certain patients. It was noted that rash and neutropenia, although not serious, have been associated with zanubrutinib. One faculty member pointed out that in a patient with neutropenia, acalabrutinib may be preferred, because zanubrutinib seems to be associated with more episodes of neutropenia. Overall, the faculty expressed that they would like to see long-term follow-up of PFS from the ALPINE trial, citing that the first-year curves in the ELEVATE-RR study (NCT02477696) of acalabrutinib vs ibrutinib initially separated, with the PFS at the end being “identical.”^{23,24}

STAKEHOLDER INSIGHTS

Faculty members concurred that patients who can tolerate therapy with either ibrutinib or zanubrutinib do equally well. What the ALPINE trial data reveal is that zanubrutinib is potentially better-tolerated, and, consequently, patients may be more likely to stay on therapy. Panelists remarked that 1 primary benefit regarding the safety data with zanubrutinib is that the cardiac risk appears to be significantly reduced. One participant offered a critique of the ALPINE trial for not including partial response with lymphocytosis as an end point. The faculty acknowledged that, because zanubrutinib has been associated with lower rates of atrial fibrillation and hypertension,

THE SEQUOIA TRIAL: COHORT 1 Study Design

The SEQUOIA trial (NCT0333633) is an open-label, multicenter, randomized phase 3 study evaluating zanubrutinib vs bendamustine plus rituximab in patients with treatment-naïve CLL/SLL.²¹ The first cohort of the study included 479 patients without del(17p) stratified by age, Binet stage, immunoglobulin heavy chain gene (*IGHV*) mutational status, and geographic region. Patients were randomly assigned to receive either zanubrutinib 160 mg twice daily until unacceptable toxicity or disease progression (n = 241) or bendamustine and rituximab for 6 28-day cycles (n = 238).²¹

Demographic and disease characteristics across the zanubrutinib and the bendamustine plus rituximab treatment groups were balanced with comparable median age (70.0 years vs 70.0 years), unmutated *IGHV* status (53.4% vs 52.4%), and

del(11q) status (17.8% vs 19.3%).²¹ The primary study end points included PFS and ORR as assessed by IRC, OS, and safety. CLL and SLL responses were assessed according to modified iwCLL guidelines and Lugano criteria. The assessment also included AEs until disease progression.²¹

Results

Key efficacy results showed that at a median follow-up of 26.2 months, estimated 24-month PFS by IRC was higher in the zanubrutinib arm (85.5%; 95% CI, 80.1%-89.6%) compared with the bendamustine plus rituximab arm (69.5%; 95% CI, 62.4%-75.5%). Likewise, ORR by IRC was higher in the zanubrutinib arm (94.6%; 95% CI, 91.0%-97.1%) vs the bendamustine plus rituximab arm (85.3%; 95% CI, 80.1%-89.5%). Estimated 24-month OS was 94.3% (95% CI, 90.4%-96.7%) in the zanubrutinib group and 94.6% (95% CI, 90.6%-96.9%) in the bendamustine plus rituximab group.²¹

In the zanubrutinib arm of the study, any-grade AEs were experienced by 93.3% of patients, and 52.5% of patients experienced an AE of grade 3 or higher. Among patients in the bendamustine plus rituximab arm, 94.3% experienced any-grade AEs, with 74.4% experiencing an AE of grade 3 or higher.²¹ AEs of interest in patients receiving zanubrutinib and those given bendamustine plus rituximab included any-grade atrial fibrillation (3.3% vs 2.6%), any-grade bleeding (45.0% vs 11.0%), bleeding of grade 3 or higher (3.8% vs 1.8%), any-grade hypertension (14.2% vs 10.6%), any-grade infection (62.1% vs 55.9%), infection of grade 3 or higher (16.3% vs 18.9%), any-grade neutropenia (15.8% vs 56.8%), and neutropenia of grade 3 or higher (11.7% vs 51.1%). Treatment discontinuation

due to AEs occurred in 8.3% of patients receiving zanubrutinib vs 13.7% of patients receiving bendamustine plus rituximab; 85.5% of patients receiving zanubrutinib remain on treatment. AEs leading to death occurred in 4.6% of patients receiving zanubrutinib vs 5.3% of patients receiving bendamustine plus rituximab, and no sudden deaths were reported.²¹

PHASE 2 TRIAL OF ZANUBRUTINIB IN BTKI-INTOLERANT PATIENTS

Study Design

An ongoing phase 2 multicenter study (NCT04116437) is evaluating the safety and efficacy of zanubrutinib monotherapy in patients with previously treated B-cell malignancies who have become intolerant to prior BTKi therapy.^{25,26} Two cohorts are included in the study design: cohort 1 includes patients who are intolerant to ibrutinib, and cohort 2 includes patients intolerant to acalabrutinib and ibrutinib.²⁵ Patients with documented disease progression during prior BTKi therapy were excluded from the study.²⁵ The recurrence of AEs associated with BTKi intolerance were assessed for severity, seriousness, and association to zanubrutinib as well as for needed dose reductions, holds, or discontinuations.²⁵

Results

At data cutoff on June 7, 2021, a total of 57 patients (CLL/SLL, 44 patients; Waldenström macroglobulinemia [WM], 9 patients; mantle cell lymphoma [MCL], 2 patients; MZL, 2 patients) were enrolled in cohort 1, and 7 patients (CLL, 4 patients; WM, 1 patient; MCL, 1 patient; MZL, 1 patient) were enrolled in cohort 2.^{25,26} All patients received at least 1 dose of zanubrutinib, and the median duration of treatment for cohort 1 was 8.7 months (range, 0.6-17.9) and for cohort 2 was 8.2 months (range, 6.4-11.4).²⁵ At data cutoff, 54 patients remained on therapy, with reasons for

discontinuation including AEs (n = 4), disease progression (n = 4), physician decision (n = 1), and withdrawal of consent (n = 1).²⁵ Interim data results showed that 73% of patients did not experience a recurrence of AEs related ibrutinib or acalabrutinib intolerance, and 79% of reoccurring AEs were noted to be of a lower grade of severity.²⁵

Safety data demonstrated grade 3 or greater AEs in 18 patients (28%) and serious AEs in 7 patients (11%). Dose interruptions and reductions secondary to AEs occurred in 17 (27%) and 3 (5%) patients, respectively.²⁵ Moreover, continued and improved responses with zanubrutinib treatment were observed in 41% and 53% of patients, respectively, with a total disease control rate of 94%.²⁵

STAKEHOLDER INSIGHTS

The majority of the faculty expressed that the predominant role of zanubrutinib has been in the setting of BTKi intolerance (primarily with ibrutinib), and they agreed that it has been well-tolerated by most patients. Experts among the panel explained that, when selecting between acalabrutinib and zanubrutinib, acalabrutinib's interaction with PPIs and potential for headache may slightly hinder its utility, and, consequently, zanubrutinib is often favored in this clinical scenario. One participant pointed out that another relevant consideration is that zanubrutinib can be dosed up to twice daily, which could pose an increased challenge for adherence to therapy in some patients. Acknowledging that zanubrutinib has been incorporated into National Comprehensive Cancer Network CLL treatment guidelines, some of the faculty would be more

inclined to use zanubrutinib when it is approved in patients with CLL, because they prefer not to have to obtain payer approval for off-label use.

THE ROLE FOR PIRTOBRUTINIB AND NONCOVALENT BTKIS

Despite the key role of BTKis in transforming the treatment landscape for CLL and other B-cell malignancies, the development of resistance and BTKi intolerance is a growing challenge.^{27,28} Acquired mutations in the *BTK* and *PLCG2* genes occur in patients receiving prolonged ibrutinib therapy; they are associated with the development of resistance to therapy with covalent BTKis.^{13,30} The most common cause of treatment resistance is the C481 mutation, which involves a cystine-to-serine substitution in the binding site region of BTK that results in a subsequent decrease in binding affinity of ibrutinib.^{13,30,31} Consequently, the development of noncovalent BTKis has ensued to provide options to overcome associated treatment limitations.¹³

Pirtobrutinib (LOXO-305) is a noncovalent, or reversible, BTKi that possesses equivalent potency for both wild-type and C481-mutated *BTK* variants.^{13,27} The inherent design of pirtobrutinib achieves greater selectivity and exposure of the BTK receptor, which allows for reduced off-target toxicity and more stable inhibitory action throughout the dosing period.²⁷ With observed decreases in the potency of covalent BTKis against C481-mutated BTK receptors, pirtobrutinib may offer a potential strategy in overcoming resistance to BTKi therapy.^{13,31}

THE BRUIN TRIAL

Study Design

The BRUIN trial (NCT03740529) is an open-label, multicenter phase 1/2 study investigating pirtobrutinib in patients with previously treated CLL, SLL, or non-Hodgkin Lymphoma.²⁹

Phase 1 of the trial included dose escalation and expansion evaluations for pirtobrutinib mono- and combination therapy.^{27,29} In phase 2, patients were enrolled into 1 of 6 cohorts according to B-cell malignancy, previous therapies, and *BTK* mutational status.^{27,29} Patients with B-cell malignancy and at least 2 prior lines of therapy were eligible for the study; however, those with CLL or SLL and only 1 previous line of therapy that included a covalent BTKi were also allowed to participate.²⁷ ORR assessed by IRC was the primary end point for the study, and key secondary end points included investigator-assessed ORR, best overall response, DOR, PFS, OS, and safety.²⁷

Results

A total of 323 patients were enrolled between March 21, 2019, and September 27, 2020, including 170 with CLL or SLL, 61 with MCL, 26 with WM, and 66 with other B-cell lymphomas.²⁷ The median number of prior therapies was 3 (range, 2-5), with the most common treatments among patients with CLL or SLL including anti-CD20 antibody (90%), BTKi (86%), chemotherapy (82%), BCL2 inhibitor (34%), or PI3K inhibitor (21%).²⁷ Of the 139 patients with CLL or SLL who were eligible for efficacy evaluation, ORR across all dose levels was 63% (95% CI, 55%-71%); in patients who had received prior treatment with a BTKi (n = 121), ORR was 62% (95% CI, 53%-71%).²⁷ For patients with del(17p) *TP53* mutations (n = 28), the reported ORR was 79%.²⁷

The most common any-grade AEs included fatigue (20%), followed by diarrhea (17%) and contusion (13%).²⁷ Neutropenia was the most common AE of grade 3 or higher, occurring in 10% of patients, and it was not dose dependent.²⁷ Notable AEs of special interest included bruising, rash, and atrial fibrillation or flutter and were associated with low occurrence rates at grade 1 (15%, 9%, and 0%, respectively) and grade 2 (2%, 2%, and 1%, respectively).²⁷

STAKEHOLDER INSIGHTS

Regarding the data surrounding pirtobrutinib, the faculty remarked that this agent appears to be associated with minimal AEs as well as relatively few grade 3 and 4 toxicities. With promising efficacy observed in patients who are double-refractory to BTKi and BCL2 inhibitor treatment, as well as those refractory to PI3K inhibitors, the faculty commented that pirtobrutinib may also play a role in filling unmet needs in the current treatment landscape. Panelists acknowledged that pirtobrutinib may become a preferred agent for double-refractory patients and highlighted that it may also be considered as a viable option in patients who have failed multiple lines of therapy. Increased therapeutic options in patients who experience relapse secondary to the development of mutations in response to treatment was emphasized as a current need, and experts opined that this is the likely setting for which pirtobrutinib would be utilized in the case that FDA approval is granted. Some of the faculty expressed concerns about using pirtobrutinib in earlier lines, underscoring the potential for resistance mutations to arise during treatment, which could lead to limited treatment options for subsequent therapy. Overall, members of the panel are anticipating additional long-term efficacy data and potential approval of pirtobrutinib.

NOVEL APPROACHES: BTKI PLUS VENETOCLAX

The highly selective BCL-2 inhibitor venetoclax continues to play a key role in the evolving treatment paradigm for CLL.³² Clinically significant tumor

lysis syndrome has been observed with venetoclax, but careful monitoring, prophylactic strategies, and dose ramp-up periods have been effective mitigation strategies.^{6,33} Results from clinical trials have demonstrated the efficacy of venetoclax as a monotherapy and in combination with other therapies in patients with CLL, and durable responses were achieved in those with del(17p)/TP53 mutations. Venetoclax offers expanded therapeutic options for patients with high-risk disease as well as younger, fit patients who may benefit from a more intensive treatment approach.^{6,9,32}

Several ongoing trials, including CAPTIVATE (NCT02910583), GLOW (NCT03462719), and SEQUOIA (cohort 3), are investigating the use of venetoclax in combination with BTKis for CLL.^{18,34,35}

THE CAPTIVATE TRIAL

Study Design

The CAPTIVATE trial is a multicenter, international phase 2 trial investigating first-line ibrutinib plus venetoclax for CLL in minimal residual disease (MRD) and fixed-duration cohorts.^{35,36}

A total of 164 patients received initial fixed-duration treatment of 3 cycles of ibrutinib followed by 12 cycles of combination therapy with ibrutinib plus venetoclax. In the primary analysis of the MRD cohort occurring during cycle 16, patients with confirmed undetectable MRD (uMRD) were randomly assigned 1:1 to receive placebo or continue ibrutinib; those who did not meet confirmed uMRD criteria were randomly assigned 1:1 to receive ibrutinib monotherapy or continue ibrutinib plus venetoclax combination therapy. The 2-year disease-free survival (DFS) rate in patients with confirmed uMRD, investigator-assessed best response per iwCLL, investigator-assessed PFS, and AEs were key end points for the study.



Notably, high-risk features including unmutated IGHV, del(17p)/TP53 mutations, complex karyotype, and del(11q) without del(17p) were present in 60%, 20%, 19%, and 17% of patients, respectively.³⁶

Results

Two-year post-randomization DFS results from the MRD cohort were presented at the 2021 American Society of Hematology annual meeting. For patients with confirmed uMRD, there were no statistically significant differences in the 2-year and estimated 3-year DFS rates between treatment groups (95% placebo arm vs 100% ibrutinib arm; 95% CI, -1.6 to 10.9; $P = .1573$). In the additional year of follow-up since the 1-year DFS primary analysis, no new DFS events occurred in patients with confirmed uMRD randomly assigned to ibrutinib or placebo. Greater improvements in best uMRD and complete response (CR)/CR with incomplete bone marrow recovery rates were observed in patients without confirmed uMRD receiving ibrutinib plus venetoclax vs ibrutinib post-randomization.³⁶

Across treatment arms, modest differences in the occurrence of AEs were observed post-randomization. The most frequent AEs of grades 3 or 4 included neutropenia, hypertension, thrombocytopenia, and diarrhea, occurring at rates of 36%, 10%, 5%, and 5%, respectively. During the 48-month treatment period, AEs contributed to treatment discontinuation of ibrutinib or venetoclax in 13% of patients.³⁶

THE GLOW TRIAL

Study Design

The GLOW trial is an open-label, phase 3 study evaluating the combination of ibrutinib plus venetoclax or chlorambucil plus obinutuzumab for the first-line treatment of patients with

CLL or SLL.^{34,37}

Patients were randomly assigned to receive either ibrutinib plus venetoclax ($n = 106$) or chlorambucil plus obinutuzumab ($n = 105$), and those with del(17p) or known TP53 mutations were excluded from the study.³⁷ Primary and secondary end points for the study were PFS by IRC assessment and MRD (uMRD; $< 10^{-4}$), respectively.³⁷ Median follow-up for the study was 27.7 months (range, 1.7-33.8).³⁷

Results

Resultant data demonstrated both peripheral blood and bone marrow uMRD rates to be significantly higher for the ibrutinib plus venetoclax group vs the chlorambucil plus obinutuzumab group (51.9% vs 17.1% [$P < .0001$] and 54.7% vs 39.0% [$P = .0259$], respectively).³⁷ Approximately 65.9% (27 of 41 patients) of patients achieved a CR or CR with incomplete bone marrow recovery in the ibrutinib plus venetoclax arm vs 33.3% (4 of 12 patients) in the chlorambucil plus obinutuzumab arm, with partial responses achieved in 54.9% (28/51) vs 16.9% (13 of 77 patients) of patients in each arm, respectively.³⁷ During the initial 12 months following the end of therapy, PFS by MRD status at 10^{-4} for patients receiving ibrutinib plus venetoclax was over 90% for patients with uMRD or detectable MRD.³⁷ Conversely, patients receiving chlorambucil plus obinutuzumab with detectable MRD relapsed more rapidly than did those with uMRD.³⁷

THE SEQUOIA TRIAL: COHORTS 2 AND 3 Cohort 2

In a second cohort of the SEQUOIA trial, patients who had CLL/SLL with centrally confirmed del(17p) were included in a nonrandomized group that was assigned to treatment with zanubrutinib.^{21,38,39} These 109 patients received 160 mg of zanubrutinib

twice daily for 3 months. At a median follow-up of 18.2 months, the best ORR was 94.5% and 18-month PFS, DOR, and OS were 88.6% (95% CI, 79.0-94.0), 84.0% (95% CI, 67.5-92.6), and 95.1% (95% CI, 88.4-97.9), respectively.^{38,39} With extended follow-up, AEs of grade 3 or higher included neutropenia/neutrophil count decrease (12.9%) and pneumonia (3.7%).³⁹

Cohort 3

The third cohort of the SEQUOIA trial includes patients with del(17p) CLL/SLL who had been nonrandomly assigned to treatment with zanubrutinib 160 mg twice daily for 3 months as a part of the second cohort study.³⁸ Following this treatment, patients in the third cohort study were initiated on combination therapy that included a continuation of zanubrutinib plus an initial ramp-up cycle of venetoclax followed by a dose of 400 mg daily. Combination therapy was given for a duration of 12 to 24 cycles until

unacceptable toxicity, progressive disease, or achievement of uMRD by flow cytometry occurred. As of June 2021, 35 of the intended 80-patient cohort had been enrolled.³⁸ Initial safety and tolerability, including the risk of tumor-lysis syndrome at baseline and before beginning treatment with venetoclax, were evaluated. Response assessment for CLL and SLL were performed according to modified iwCLL criteria and Lugano criteria.³⁸

The initial efficacy evaluation of 3 months after initiation of zanubrutinib had been reached by 31 patients. ORR in these patients was 96.8% (30 patients).³⁸ At the time of data cutoff, 29 patients had begun combination therapy, and 27 had completed the ramp-up dosing of venetoclax. With a median follow-up of 9.7 months, AEs were experienced by 82.9% of patients, and serious AEs were observed in 11.4% of patients. Common AEs reported in at least 10% of patients included diarrhea, neutropenia, fatigue, nausea, and petechiae (5, 5, 4, 4, and

4 patients, respectively).³⁸ AEs of grade 3 or higher were observed in 37.1% of patients, of which neutropenia and diarrhea were the most common (4 and 2 patients, respectively). Grade 3 atrial fibrillation was reported in 1 patient who presented with ongoing grade 2 atrial fibrillation at baseline. At the data cutoff, no tumor lysis syndrome AEs were seen.³⁸

STAKEHOLDER INSIGHTS

There was consensus among panel experts that continuous therapy can be a significant burden for patients, particularly for younger individuals, and combination therapy with zanubrutinib and venetoclax offers the opportunity of treatment discontinuation. Faculty members highlighted that using the MRD-based approach for maintenance therapy helps to more easily determine which patients really need maintenance therapy and, if so, what kind of

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maintenance therapy. One participant offered that combination therapy with a B cell-receptor antagonist and venetoclax is the most powerful combination and is an option that should be considered for patients with del(17p)/TP53 mutations, or complex karyotypes. Another expert expressed that this combination would offer an all-oral regimen, which may be appealing for some patients and could allow a greater number of patients to receive treatment with venetoclax.

LOOKING AHEAD AND KEY TAKEAWAYS

In terms of looking ahead, the faculty agreed that targeted agents have, in many cases, replaced the use of chemotherapy and have shifted the approach of how CLL is treated. As new agents and combinations are incorporated into the treatment landscape, additional data on the sequential use of these treatments will be critical. Panelists also expressed their anticipation for data that may provide greater insight regarding treatment options for patients who are double-refractory, and they expressed interest in having these options available outside the clinical trial setting. Additionally, experts look forward to seeing how the MRD-based approach can be used to guide treatment goals and individual treatment decisions. In closing, the panel remarked that a fair amount of chemotherapy continues to be used in community practices. Importantly, emerging data on novel agents and treatment strategies that demonstrate improved outcomes should be shared with community oncologists. ■

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Expert Perspectives on the Evolving Role of BTK Inhibitors for the Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia



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INTRODUCTION

Treatment for chronic lymphocytic leukemia (CLL) has traditionally involved chemoimmunotherapy regimens; however, the emergence of novel targeted therapies has shifted the overall treatment paradigm. As new treatment approaches using targeted agents have emerged, so, too, have new challenges associated with treatment selection and therapeutic decision-making. Research into the Bruton tyrosine kinase inhibitors acalabrutinib and zanubrutinib have prompted clinicians to reassess their therapeutic decision-making in the relapsed/refractory setting. Ahead, Richard R. Furman, MD; Benjamin Heyman, MD; and Shuo Ma, MD, PhD; discuss these and other aspects of the evolving treatment landscape of CLL.

**Interview transcripts are edited for readability.*

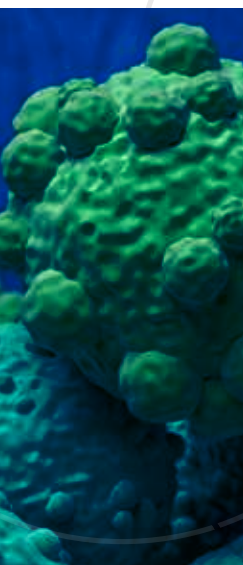
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OncLive®: What is your current strategy for treatment selection in relapsed/refractory chronic lymphocytic leukemia (CLL)?

HEYMAN: We're fortunate enough that right now in CLL, we have a plethora of treatment options, so in the relapse setting, it depends on what patients were initially administered. For most patients with CLL, we've moved away from chemoimmunotherapy (CIT) approaches. But if someone 10 or 15 years ago got CIT and [now has] relapsed disease that requires treatment, then we're going to be looking at factors, such as their cytogenetics, [and] high-risk factors, such as 17p deletion. Do they have an immunoglobulin heavy chain that's unmutated or other cytogenetic high-risk features or genomic high-risk features?

In general, I'd say that I think it's a discussion with patients. Right now, the current treatment

paradigm, [which] may be changing a bit, is fixed-duration therapy with venetoclax and an anti-CD20 monoclonal antibody for either 1 or 2 years or continuous therapy with a BTKi (Bruton tyrosine kinase inhibitor). We are going to be looking at factors such as comorbidities. Do they have evidence of cardiac disease or other comorbidities that would make you a bit concerned about giving them a BTKi? [For] patient preference, do they prefer a fixed-duration or a chronic therapy? I think the other option to think about for patients nowadays is the risk of infection. With venetoclax-based regimens, we're typically administering them in combination with an anti-CD20 monoclonal antibody, and that really does put patients at higher risk for a coronavirus [disease 2019 (COVID-19)] infection, so I think many of us would prefer, if we can, to give them a BTKi.



OncoLive®: How does the treatment selection in the frontline setting impact therapeutic decision-making in the second-line setting?

FURMAN: My treatment selection for relapsed/refractory CLL is going to be very dependent upon the treatment that was used as frontline therapy and how the patient tolerated and responded. In patients who are on a BTKi and are progressing, I'll often add venetoclax to the BTKi to take advantage of synergy. Treating them earlier then would be indicated by iwCLL (International Workshop on CLL) criteria, in order to avoid letting the patients develop high tumor burdens and the risks of tumor lysis [syndrome]. Especially in patients who are progressing on BTKis, where there is this risk of the patient having rapid progression with discontinuation of the BTKi, it becomes important to make sure that the next therapy, if it's not going to overlap, at least is lined up to start as soon as you do stop that therapy.

For those patients who received venetoclax as their first-line therapy, if they had a significant response duration, typically greater than 2 years, I will be inclined to start the venetoclax again—once again, starting before they develop a high tumor burden in order to avoid the risks of tumor lysis syndrome. In patients who have progressed on venetoclax with a really short response duration, I will switch to the BTKi and hope to provide long-term disease control.

HEYMAN: If a patient has received a BTKi or a venetoclax-based regimen frontline, then, in the relapse setting, I'm typically switching from 1 class to the other. If they first received venetoclax and an anti-CD20 monoclonal antibody and had a great response for a very long period of time, then we may want to consider retreatment just because we expect them to hopefully also have a really great response. We're lucky that there are lots of options, and it's an ongoing patient-physician discussion about that.

MA: You want to see what the reason [was for] the medication failing patients in the frontline treatment. Some patients might have intolerance, and some patients may be having true progression, so that will be quite different. For example, if a patient is having intolerance to a first-generation BTKi, they can still continue the BTKi pathway but use a second-generation [agent]. For a true progression, we would have to switch class.

OncoLive®: What information does the ALPINE trial and its data provide you with when looking at treatment selection for CLL?

FURMAN: The ALPINE study investigated ibrutinib vs zanubrutinib in patients who had relapsed/refractory CLL, and [it] demonstrated that zanubrutinib had a higher overall response rate (ORR) compared with ibrutinib. I think the data need to be interpreted very carefully, in part because progression-free survival (PFS) as a surrogate for overall survival is really what's most important to our patients and

us, and this study used ORR, which did not include partial response with lymphocytosis. So in essence, I think the ORRs are probably a lot closer than what this study reports out and, in fact, may not reach statistical significance.

One thing that is most important when you look at the ORR is the ability for patients to benefit from therapy. It's so dependent on their ability to stay on therapy, so some of the differences in responses are definitely due to patients discontinuing therapy due to adverse events. Zanubrutinib proved itself to be better-tolerated and enabled more people to stay on therapy, so that's really the most important aspect. The other aspect that I think is particularly worth knowing is the lower risk of atrial fibrillation, which is something that, out of all the [adverse] effects associated with BTKis, is probably the 1 that I find most worrisome and most important to avoid.

HEYMAN: The ALPINE trial looked at zanubrutinib in the relapsed setting for patients with CLL, and we expect zanubrutinib is going to be approved soon. It can be very effective. We're looking at ibrutinib, acalabrutinib, and now, zanubrutinib. Zanubrutinib appeared to have an improvement in PFS over ibrutinib. From a head-to-head standpoint, we've already had an acalabrutinib vs ibrutinib head-to-head [study] and didn't see much of a difference in improvement in survival, but here, we see that there is some improvement—not huge—but a definite improvement in PFS in zanubrutinib.

MA: The ALPINE study is an important phase 3 trial that is giving [us] a head-to-head comparison between the second-generation BTKi zanubrutinib vs the first-generation BTKi ibrutinib, so it gives us a direct comparison of the efficacy and the toxicity profile. I think it is very helpful to look at the same patient population that's randomized. Then you can really truly compare the efficacy and toxicity.

OncoLive®: What is your interpretation of the safety profile of zanubrutinib compared with other BTKis? How do these drugs' safety profiles factor into your therapeutic decision-making?

FURMAN: BTKis are extremely well-tolerated, but acalabrutinib and zanubrutinib are much better tolerated than ibrutinib is. Between zanubrutinib and acalabrutinib, there are some significant differences in their tolerability. Acalabrutinib has bruising and headaches as its primary [adverse] effects, and I believe zanubrutinib predominantly has neutropenia and rash as its [adverse] effects. Choosing the agent that's going to be best for the patient enables us to increase the likelihood of our patients being able to remain on therapy and derive benefit. Of course, [it is important to] remember that acalabrutinib has the issue related to [patients] not being on a proton pump inhibitor, because you need the low pH in the stomach to improve its solubility.

MA: Compared with ibrutinib, we do see an improved toxicity profile [with zanubrutinib], most remarkably the



Richard R. Furman, MD

“I do believe that the 3 BTKis are all equally effective, and the greatest thing about zanubrutinib and acalabrutinib is their tolerability.”

cardiac risk. There's a significant reduction of the cardiac risk of patients, fortunately, with zanubrutinib compared with ibrutinib. Currently, there [are] no comparative data between zanubrutinib and acalabrutinib. Both are second-generation BTKis, so both are more selective in inhibiting BTK and have fewer off-target effects, but we don't know the comparison between the 2 [agents].

OncoLive®: What have been your experiences integrating zanubrutinib into your clinical practices?

FURMAN: I have used zanubrutinib very frequently in my practice, for all my patients with low-grade lymphomas. I do believe that the 3 BTKis are all equally effective, and the greatest thing about zanubrutinib and acalabrutinib is their tolerability and [ability] to keep people on [treatment]. That's really what drives my choice of those 2 [agents]. My experiences with zanubrutinib have been very good, with the biggest issue being rash, which has really been the only reason why I've had to discontinue treatment in patients. We do see neutropenia with zanubrutinib, but it's typically not significant enough that we would have to withhold therapy or change treatment. I do find the headaches somewhat of a problem for many patients with acalabrutinib. Zanubrutinib affords an opportunity to treat these patients without the risks of headaches, and it also avoids the issue of the patient needing to be off of protein pump inhibitors. It often becomes the drug that I commonly reach for.

HEYMAN: I certainly use zanubrutinib quite a bit. It's approved for several different lymphoid malignancies already—Waldenström [macroglobulinemia], mantle cell lymphoma. It's already on the NCCN (National Comprehensive Cancer Network) guidelines for patients with CLL and will likely get approval shortly. In general, I find zanubrutinib to

be a very good, effective drug. It's very well-tolerated, and patients have not had too many significant [adverse] effects.

In my practice, I believe that BTKis are really the first choice therapy for all patients with low-grade lymphomas in those I'm not going to treat with an anti-CD20 [agent]. Among the BTKis, the second generation affords so much better tolerability than ibrutinib does, [so] those are usually the agents that I'm going to reach for. When I choose to use zanubrutinib as compared with acalabrutinib, it's typically going to be based on the need to administer therapy to someone who is on the proton pump inhibitor or someone who seems to have a particularly difficult time with headaches.

I do notice that compared with other BTKis, zanubrutinib does seem to have increased risk of neutropenia, but, in general, my experience has been very positive. Patients are able to take the drug and stay on the drug. I think that's the most important thing we see with BTKis in general. Patients will get typical adverse effects, whether it's gastrointestinal [adverse] effects, bleeding or bruising, [or] maybe muscle aches. With acalabrutinib, patients may get a headache. But if you can get patients through that first 3 to 6 months or so and work through those potential adverse effects, then they really have a great chance to be able to stay on drug for long-term. We know that the discontinuation rate of BTKis is much less after 1 year, so if we can get them through those first 6 months to a year, then, typically, they could have excellent disease control long-term with these medications.

MA: I have used this agent in my practice, in patients who had intolerance to ibrutinib but are still benefiting from the inhibition of the BTK pathway. I have used zanubrutinib, especially for a patient who may not be a candidate for acalabrutinib. For example, if someone has to stay on a proton pump inhibitor and needs the long-term antacid medication,

I use zanubrutinib. My experience so far has been quite favorable. Patients have been tolerating treatment fairly well. If a patient is having cardiac risk factors or has an underlying cardiac structural abnormality, congestive heart failure, or a high risk for arrhythmia, then they wouldn't be a candidate for acalabrutinib. There are particular groups of patients that will really benefit from zanubrutinib, but, if they are not in that category, I think [there] is equal benefit from all of the BTKis available.

OncoLive®: What are your impressions of the SEQUOIA trial? In what ways might its key data affect your clinical decision-making in CLL?

FURMAN: The SEQUOIA trial looked at zanubrutinib in different circumstances using 3 different cohorts. The first cohort looked at zanubrutinib vs bendamustine plus rituximab. It showed, as would be expected based upon our earlier data with ibrutinib and other agents, that zanubrutinib is more efficacious, with an improvement in PFS as well as an improvement in tolerability. The ability to keep people on therapy and continue to control their disease long-term is so important. It showed that zanubrutinib is tolerable, with a low risk of atrial fibrillation and other drug-induced adverse events that require discontinuation, [which] demonstrated that it's a therapy that patients will be able to stay on. The second cohort from the SEQUOIA study looked at zanubrutinib in patients with 17p deletion (a deletion in the short arm of chromosome 17p), and this, of course, is a very difficult patient population to treat. It really showed that zanubrutinib is effective in patients with 17p deletions, and that, of course, is very important, because they represent the hardest patients we have to treat.

HEYMAN: The first arm of the SEQUOIA trial looked at zanubrutinib vs conventional CIT, and we saw an improvement in survival. Again, this is not unexpected. We know BTKis have superior efficacy and adverse effect profile compared with conventional CIT for patients with CLL, but I think it's a good proof of principle demonstrating that. I think the other arms of this study are interesting, specifically looking at zanubrutinib in patients with high-risk features, such as some with 17p deletion. The study is also looking into those types of combination approaches with venetoclax. We see that in patients with 17p deletion, zanubrutinib seems to have good efficacy in getting disease control and PFS similar to what we see with ibrutinib. As we move forward, we've seen studies like the CAPTIVATE study [of] the combination of ibrutinib and venetoclax in a fixed-duration treatment. [We are] looking into those types of combination approaches where we can maximize the BTKi but maybe not have to put patients on chronic therapy. If we can potentially give it as an all-oral combination strategy and give it as a time-limited treatment, then, if a patient were to have recurrence 4 or 5 years later, we may

potentially be able to retreat them with the same time-limited treatment. I think we'll see how that third arm of the combination of venetoclax and zanubrutinib plays out, but I think that's also going to be a promising treatment strategy for patients. Typically, venetoclax is given with the anti-CD20 monoclonal antibody. These are infusions; patients are preferring not to get infusions if they can. We worry about the immunosuppression. In the setting of COVID-19, we don't know what kind of other potential pandemics or other infections might arise, so I think that's 1 of the biggest fears we have for patients with CLL.

MA: The SEQUOIA trial is a multiple-arm study. Arms A and B have a randomized design comparing zanubrutinib monotherapy with a conventional immunochemotherapy combination with randomized rituximab. In these settings, zanubrutinib is showing significant benefit in prolonging PFS, which is providing another piece of evidence that targeted therapies overall have outperformed the conventional CIT, becoming 1 of the new standards of care in the treatment of CLL.

The other arms, arm C and arm D, are not randomized, so those are just single-arm portions. Arm C is looking at patients who have a *TP53* mutation or 17p deletion being treated with zanubrutinib monotherapy. The initial data definitely show encouraging results that zanubrutinib is a very effective agent even in this area of high-risk CLL population. R&D [research and development] is interested in using a combination of the zanubrutinib with venetoclax targeting 2 pathways: BTK and the BCL2. Early data are showing very encouraging results that this combination is also highly effective in this high-risk population. The study is also expanding into including patients who do not have those *TP53* alterations, so [these are] more of the standard patients with CLL. We're waiting to see those results.

OncoLive®: What are some key treatment considerations when selecting therapy in the frontline setting?

MA: There are a number of factors that we'll consider. One is the patient's comorbidities and fitness. For example, we know that BTKis do have a class effect of toxicities including potential cardiac risk, potential bleeding risk, and hypertension. When we have a patient who has a higher cardiac or significant bleeding risk, we'll think about either using a second-generation BTKi or using a different class.

For example, if they have a potential bleeding disorder or if they are on dual antiplatelet agents after cardiac stenting, adding a BTKi that is an antiplatelet agent will significantly increase the risk of bleeding. That's the situation I will try to avoid in the use of BTKis but where I rather favor the use of BCL2 inhibitor venetoclax with anti-CD20 monoclonal antibody.

We're really thinking about either a BTKi as 1 option or the venetoclax plus an anti-CD20 [monoclonal antibody]. When

choosing venetoclax and an anti-CD20 [agent], 1 factor we are concerned about is risk of tumor lysis syndrome. If you have a patient [who] has significantly impaired renal function that would make them not able to handle the tumor lysis as well, I'll be cautious using the BCL2 inhibitor in that perspective. For most patients, it really comes down to discussion with the patient about patient preference and convenience. Some patients really do not like much disruption of their working schedule, and they would rather stay on a BTKi. Instead of having an indefinite treatment like a BTKi, some patients would like to have a more defined period of treatment. Patient preference and personal need also play into decision-making, because it's really a discussion between the treating physician and the patient.

OncoLive®: Looking forward, are you anticipating any clinical trials or emerging treatments on the horizon? What do you anticipate for the future of CLL treatment?

FURMAN: The next approval that I expect in CLL will be zanubrutinib, in all likelihood. It really will increase our options for treating our patients with CLL. After zanubrutinib, other treatment options that I think will be significant additions to our armamentarium include the use of pirtobrutinib, which is a reversible BTKi, as well as umbralisib, which is a PI3K (phosphatidylinositol 3-kinase) inhibitor that is less likely to lead to autoimmune phenomena. Both can help provide additional agents for treating our patients with CLL. It will be important to identify whether pirtobrutinib is an extremely well-tolerated BTKi with no advantage over the covalent BTKis or whether it really does have an advantage. The truth is that we've seen some data about its efficacy in patients who have

progressed on covalent inhibitors. The question is, are these patients going to do better if they were to get it instead of the covalent BTKis?

I think the future is very bright for patients with CLL. My real vision of the future is that patients are really going to be divided into 2 groups: 80% of patients will do extremely well with just single-agent BTKi therapy, and those are typically the people who do not have a complex karyotype, 17p deletion, *TP53* mutation, a notch mutation, or a karyotype V gene. The other 20% are people who will have something of those [and] will benefit from either early intervention or combination therapy of a BTKi plus venetoclax to get rapid control of their disease and to bring their disease down very deeply. Giving everyone combination therapies early on will also improve the ability to control everyone's disease with fixed-duration therapy, and I suspect that we'll see a benefit, which is probably very important in the era of COVID-19, in terms of preserving the immune system.

HEYMAN: I think we're very lucky right now, because we've had such great success with the BTKis as a class as well as venetoclax as a drug. Most patients, 80% to 85%, will be great. There is a select handful of patients where we're starting to see evidence of what we call double-refractory [disease], where they progress on a covalent BTKi, and they've also progressed on a venetoclax-based regimen. That is a difficult place to be when it comes to managing a patient, and our treatment options are limited. Our current standard-of-care treatment options, such as PI3K inhibitors or CIT, are not very effective in this space, so we certainly need to have better treatments for them. Fortunately, we have several in development. I think [a] notable one [is] going to be a noncovalent BTKi drug called pirtobrutinib. It can really get



Benjamin Heyman, MD

“There are a select handful of patients where we're starting to see evidence of what we call double-refractory [disease]...We certainly need to have better treatments for them.”

excellent disease control in about two-thirds to three-quarters of patients. It can also be fairly durable and has an excellent adverse effect profile. Because it's a noncovalent BTKi, its mechanism of action is a little bit different than our covalent BTKis. The most common mutation that we'll see for a patient with a covalent agent being this [BTK] *C481S* mutation, we can see that the noncovalent agents are able to overcome that based on the site of binding. I think that's going to be a great opportunity for patients. We'll have to see how we fit in noncovalent BTKis. Right now, they're being actively studied in this post-covalent BTKi space, but we may have to think about using them beforehand. I think those studies are going to have to be assessed.

The second really big advancement right now is going to be looking at CAR [chimeric antigen receptor] T-cell therapy or cell therapy for patients with CLL. Certainly, not everybody needs CAR T-cell therapy, but I think there are going to be patients, especially this double-refractory [population] or patients post-BTKi for whom CAR T-cell therapy will be beneficial. We've seen that the product lisocabtagene maraleucel with or without acalabrutinib seems to be able to produce excellent responses: high response rates, long

PFS, and high rates of undetectable MRD (minimal residual disease). Where exactly does that fit in? Is it going to be only for patients who are been treated with venetoclax and BTKis? Or are we going to think about using it earlier, potentially in patients who are having suboptimal responses as a potential consolidation?

MA: There are a lot of exciting things going on. Currently in relapsed/refractory CLL, for example, I would like to know if retreatment with venetoclax-based therapy is feasible. There are [data from] a small number of patients from prior studies that suggest that retreatment could be a potentially feasible option. For the BTKi route, we're very excited about the noncovalent BTKi that has shown exciting activity, even for patients who became refractory to the first- or second-generation BTKi. The agent has been shown to even have an improved toxicity profile, so there's something that we're really looking forward to. CAR T-cell therapy is another very exciting front. Cellular immunotherapy has been shown in some patients to produce very sustained, long-term responses even for patients who had been fairly refractory to their treatments in our center, so that's another new area to look forward to, as well. ■

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