

OncLive[®]

CHRONIC LYMPHOCYtic LEUKEMIA/
SMALL LYMPHOCYtic LEUKEMIA

SEPTEMBER 21, 2021

VIRTUAL WORKSHOP

SCIENTIFIC **INTERCHANGE & WORKSHOP**

Updates in the Treatment
of **Chronic Lymphocytic
Leukemia/Small
Lymphocytic Leukemia**

A microscopic view of cells, likely lymphocytes, rendered in shades of blue and green. The cells are spherical and have a textured, bumpy surface. A white grid of dashed lines and solid circles is overlaid on the image, creating a scientific or medical aesthetic. The background is dark blue.

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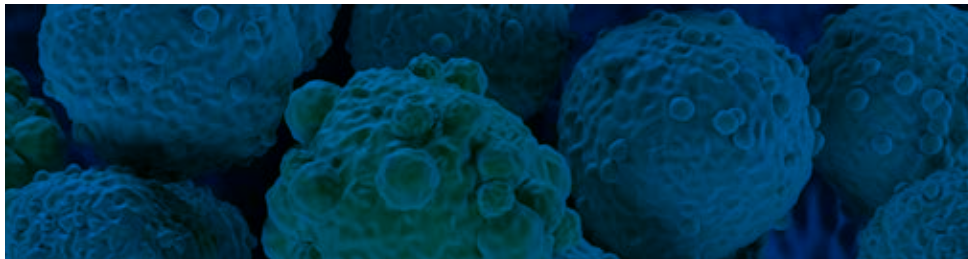
Mike Hennessy Sr



MJH Life Sciences, LLC | 2 Clarke Dr. | Suite 100
Cranbury, NJ 08512 | (609) 716-7777

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CLL/SLL



KEY TAKEAWAYS

- ▶ Bruton tyrosine kinase inhibitors (BTKis) are efficacious; however, there may be differences in potency (as assessed by rates of progression-free survival) that are demonstrated by long-term follow-up data accumulated from head-to-head clinical trials such as the ALPINE (NCT03734016) and ELEVATE-RR (NCT02477696) studies.
- ▶ When treating patients with agents that are to be taken continually and for an indefinite period of time, clinicians need to consider the effect of low-grade toxicities on patients' quality of life.
- ▶ Although second-generation BTKis are preferred over first-in-class ibrutinib, a future FDA approval of ibrutinib in combination with venetoclax may bring ibrutinib back into favor.
- ▶ The investigational BTKi pirtobrutinib (LOXO-305) appeared to be well tolerated whereas ARQ-531 may have off-target toxicities.

Updates in the Treatment of Chronic Lymphocytic Leukemia/ Small Lymphocytic Leukemia

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a monoclonal lymphoproliferative disorder in which morphologically mature, dysfunctional B-cell lymphocytes proliferate and accumulate in the peripheral blood, spleen, lymph nodes, and bone marrow.¹ Small lymphocytic leukemia (SLL) has an identical pathology and immunophenotype as CLL but is limited to the lymph nodes; thus, CLL and SLL are considered manifestations of the same disease.² CLL accounts for 25.0% to 30.0% of new cases of leukemia in the United States and mostly occurs in adults with an average age of 70 years.¹

Although no treatments are considered curative (other than, potentially, allogeneic hematopoietic stem cell transplantation [allo-HSCT]), the advent of effective, well-tolerated therapies appears to improve life spans, particularly in patients with symptomatic high-risk disease.^{1,3} Small-molecule treatment options for CLL target different mechanisms of B-cell differentiation and growth and include anti-CD20 monoclonal antibodies (eg, obinutuzumab and rituximab), the B-cell lymphoma 2 (BCL2) inhibitor venetoclax, and Bruton tyrosine kinase (BTK) inhibitors (BTKis).³ BTK is a therapeutic target of particular interest because its signaling is involved in activation of pathways involved in proliferation, trafficking, chemotaxis, and adhesion of B cells.⁴⁻⁶

On September 21, 2021, a panel of oncologists who specialize in hematologic malignancies participated in a virtual workshop to discuss strategies for management of CLL/SLL, with a focus on currently available and novel BTKis.

COVALENT BTKIS

There are 3 FDA-approved BTKis: ibrutinib, acalabrutinib, and zanubrutinib.⁴⁻⁶

For adult patients with CLL/SLL, first-generation BTKi ibrutinib is indicated as a monotherapy in both the relapsed/refractory (R/R) and frontline settings, in combination with rituximab or obinutuzumab in the frontline setting, and in combination with bendamustine and rituximab in the R/R setting.⁴

Second-generation BTKis acalabrutinib and zanubrutinib are designed to maximize occupancy of BTK binding sites and minimize off-target inhibition of kinases.⁷ For adult patients with CLL/SLL, acalabrutinib is indicated as a monotherapy in the frontline or R/R setting or in combination with obinutuzumab in the front-line setting.⁵ Results from an in vitro study showed that acalabrutinib was more selective and had less off-target inhibition than ibrutinib.⁸ The results of another study that included patients with CLL or SLL who were intolerant to ibrutinib showed that acalabrutinib led to an overall response rate (ORR) of 76.0%, and 64.0% of patients did not experience a recurrence of the adverse events (AEs) that led to intolerance of ibrutinib.⁹

Zanubrutinib is a potent, specific, highly selective, and irreversible BTKi.¹⁰ Although zanubrutinib does not yet have a CLL/SLL indication, it has FDA approval as a treatment for mantle cell lymphoma, Waldenström macroglobulinemia, and marginal zone lymphoma.⁶ Experts have hypothesized that the higher specificity of zanubrutinib reduces the toxicities caused by off-target inhibition observed with ibrutinib.¹⁰

STAKEHOLDER INSIGHTS

BTKis are effective at treating CLL/SLL, but longer-term follow-up data that compare second-generation inhibitors with ibrutinib are needed to determine the relative potency of each

drug. Given that BTKis are used continuously and indefinitely, the effects of grade 1 or 2 toxicities on a patient's quality of life (QOL) must be considered. Minimizing AEs by selecting a less toxic second-generation BTKi or reducing the dose of ibrutinib (if necessary for tolerability) may improve adherence to BTKi therapy.

FIRST-LINE TREATMENT SELECTION

Standard-of-care treatments in the first-line setting for patients with CLL/SLL include ibrutinib or acalabrutinib (with or without obinutuzumab) or a combination of venetoclax with obinutuzumab. Other commonly used regimens in this setting are fludarabine, cyclophosphamide, and rituximab (FCR), chemotherapy (particularly in patients with *IGHV* mutations), bendamustine with an anti-CD20 antibody, or chlorambucil with obinutuzumab.¹

Several clinical trials have assessed the efficacy and safety of BTKis as monotherapies or as part of combination regimens in the first-line setting for adult patients with CLL/SLL: RESONATE-2 (NCT01722487), ELEVATE-TN (NCT02475681), CAPTIVATE (NCT02910583), and SEQUOIA (NCT03336333).¹¹⁻¹⁷

RESONATE-2 Clinical Trial

In the phase 3 RESONATE-2 clinical trial, patients 65 years of age or older with previously untreated CLL/SLL without 17p deletion (del[17p]) were randomized to receive ibrutinib (the standard dose of 420 mg daily) continually until progression or development of unacceptable toxicity or up to 12 cycles of chlorambucil.¹¹

The study met the primary end point of PFS assessed by independent review committee (IRC), with an 84.0% reduction in relative risk for progression or death with ibrutinib (HR, 0.16; 95% CI, 0.09-0.28; $P < .001$). The rate of PFS at 18 months was

90.0% for patients treated with ibrutinib and 52.0% for patients treated with chlorambucil. The rate of overall survival (OS) at 24 months was higher for patients treated with ibrutinib (98.0%) than patients treated with chlorambucil (85.0%). Also, treatment with ibrutinib was associated with an 84.0% reduction in relative risk of death (HR, 0.16; 95% CI, 0.05-0.56; $P = .001$).¹¹

In this trial, the most common AE associated with ibrutinib was diarrhea, which occurred in 42.0% of patients. Other common AEs that occurred in at least 20% of patients treated with ibrutinib were fatigue, nausea, and cough. Discontinuation of treatment due to AEs occurred less frequently with ibrutinib than with chlorambucil (9.0% vs 23.0%, respectively); however, atrial fibrillation occurred in 8 patients in the ibrutinib group compared with 1 patient in the chlorambucil group.¹¹

Retrospective Study of Ibrutinib-Related Toxicities

Despite the relatively low rates of discontinuation with ibrutinib in the RESONATE-2 trial, longer term follow-up showed that up to 51.0% of patients who were taking ibrutinib in clinical trials discontinued therapy; of these, up to 32.0% occurred because of AEs.¹¹ A retrospective study based on data collected from the Connect CLL Registry evaluated rates and reasons for discontinuation in patients with CLL who were treated with ibrutinib in a clinical trial or with the commercially available drugs at 9 cancer centers in the United States.¹²

Of the 616 patients included in this study who received ibrutinib, 41.0% had discontinued the drug at a median follow-up of 17 months. The most common reason was toxicity, which accounted for 63.1% and 50.2% of discontinuations in the frontline and R/R settings, respectively. Among the most common toxicities leading to discontinuation were arthralgia (41.6%), atrial fibrillation (25.0%), and rash (16.7%) in the frontline setting and atrial fibrillation (12.3%),

infection (10.7%), and pneumonitis (9.9%) in the R/R setting. The authors stated that the higher number of toxicity-related discontinuations in the frontline setting that were noted in this study compared with the RESONATE-2 trial may indicate a lack of comfort with toxicity management among physicians, higher incidence of toxicity in clinical practice than in clinical trials, differences in patient ages and comorbidities, and a lower threshold for discontinuation because alternative treatment options are available.¹²

ELEVATE-TN Clinical Trial

The phase 3 ELEVATE-TN trial evaluated the efficacy and safety of acalabrutinib, acalabrutinib-obinutuzumab, and obinutuzumab-chlorambucil (randomized 1:1:1) in patients with previously untreated CLL.¹³

The primary end point of this study was PFS. Interim results at the median follow-up of 28 months showed that acalabrutinib-obinutuzumab was associated with a longer PFS than obinutuzumab-chlorambucil (not reached [NR] vs 22.6 months; HR, 0.10; 95% CI, 0.06-0.18; $P < .0001$). Also, PFS with acalabrutinib monotherapy was also superior to obinutuzumab-chlorambucil (median PFS, NR; HR, 0.20; 95% CI, 0.13-0.31; $P < .0001$). Improvements in PFS with acalabrutinib-containing regimens were consistent across subgroups, including those with del(17p).¹³

IRC-assessed ORR was higher with acalabrutinib-obinutuzumab than with obinutuzumab-chlorambucil (94.0% [95% CI, 89.3%-96.5%] vs 79.0% [95% CI, 71.9%-83.9%]; $P < .0001$), respectively. The ORR among patients treated with acalabrutinib monotherapy was 85.0%.¹³

The most common AEs that occurred in the acalabrutinib-obinutuzumab and acalabrutinib monotherapy arms included headache (40.0% and 37.0%), diarrhea (39.0% and 35.0%), neutropenia (31.0% and 11.0%), and nausea (20.0% and 22.0%), respectively. The most

common AEs in the obinutuzumab-chlorambucil arm included neutropenia (45.0%), infusion-related reactions (40.0%), nausea (31.0%), and diarrhea (21.0%). Rates of AEs that led to treatment discontinuation were 11.0% in the acalabrutinib-obinutuzumab arm, 9.0% in the acalabrutinib monotherapy arm, and 14.0% in the obinutuzumab-chlorambucil arm. Atrial fibrillation was reported in 3.0%, 4.0%, and 1.0% of the acalabrutinib-obinutuzumab, acalabrutinib monotherapy, and obinutuzumab-chlorambucil arms, respectively. Rates of bleeding were higher among patients treated with acalabrutinib-obinutuzumab and acalabrutinib monotherapy (43.0% and 49.0%, respectively) vs 12.0% of the obinutuzumab-chlorambucil arm.¹³

Updated data presented at the 2021 American Society of Clinical Oncology Annual Meeting showed that at a median follow-up of 46.9 months, PFS continued to be superior with acalabrutinib-containing regimens (87.0%, 78.0%, and 25.0% for acalabrutinib-obinutuzumab, acalabrutinib, and obinutuzumab-chlorambucil, respectively). Rates of atrial fibrillation were 3.9%, 6.1%, and 0.6%, and rates of bleeding were 47.2%, 41.9%, and 11.8% for the acalabrutinib-obinutuzumab, acalabrutinib, and obinutuzumab-chlorambucil arms, respectively.¹⁴

CAPTIVATE Clinical Trial

Based on preclinical data that showed ibrutinib or acalabrutinib increased the sensitivity of CLL cells to venetoclax, the multicenter, phase 2 CAPTIVATE clinical trial investigated the safety and efficacy of ibrutinib combined with venetoclax in adult patients with CLL/SLL.¹⁵

The fixed-duration cohort received 3 cycles of ibrutinib followed by 12 cycles of ibrutinib with venetoclax. The rate of complete response (CR) or CR with incomplete bone marrow recovery (CRi) in this cohort was 56.0% among patients without del(17p), which met the primary end point and was

a meaningful improvement over the historical comparator of FCR.¹⁶

Most AEs were grade 1 or 2; the most common AEs of any grade included diarrhea (62.0%), nausea (43.0%), neutropenia (42.0%), and arthralgia (33.0%). AEs of clinical interest included atrial fibrillation (4.0%) and major hemorrhage (2.0%).¹⁶

SEQUOIA Clinical Trial

The phase 3 SEQUOIA clinical trial randomized patients with previously untreated CLL/SLL without del(17p) to receive zanubrutinib or rituximab-bendamustine. Zanubrutinib monotherapy was administered to a third arm (arm C) of patients with previously untreated CLL/SLL harboring del(17p).¹⁷

The ORR was 94.5% and was consistent across prespecified demographic and baseline disease characteristics, with a duration of response (DOR) of at least 12 months in 92.8% of patients. Estimated rates of 18-month PFS and OS were 88.6% and 95.1%, respectively.¹⁷

Any-grade AEs of interest included infections (64.2%), bleeding (26.6%), bruising (24.8%), neutropenia (18.3%), diarrhea (15.6%), nausea (13.8%), arthralgia (11.0%), and fatigue (10.1%).¹⁷

The authors concluded that zanubrutinib appears to have efficacy that is favorable to that observed with chemoimmunotherapy and at least comparable with ibrutinib. The authors also stated that zanubrutinib appears to have a favorable toxicity profile, with low incidences of grade 3 AEs commonly associated with BTKis and low rates of discontinuation related to AEs.¹⁷

STAKEHOLDER INSIGHTS

Many of the panelists stated that they frequently use BTKis in the first line for patients with CLL/SLL, particularly for patients with high-risk features such as TP53 mutations or del(17p), although they noted venetoclax-

based therapy may be preferable for patients with favorable-risk disease because the duration is fixed. Patient preference and payer coverage also play key roles in the selection of frontline therapy; factors they consider include preference for continuous vs fixed-duration therapy and oral vs intravenous administration.

The ibrutinib-venetoclax combination provides a fully oral, time-limited option for therapy, but some panelists cautioned that using these 2 highly effective agents in the frontline setting may eliminate them as options in the R/R setting.

Noted benefits of continuous BTKi therapy included patient convenience, availability of long-term data, better comparators in clinical trials, and high efficacy in high-risk disease. AEs associated with BTK inhibition can interfere with continuous use, and the longer duration of therapy increases risks for major cardiac AEs.

Data from the SEQUOIA trial indicate that zanubrutinib is effective in CLL/SLL with del(17p), but the experts said that the efficacy is similar among all BTKis in this population.

TREATMENT SELECTION FOR R/R CLL/SLL

Standard-of-care therapeutic options in the second line and beyond for patients with CLL/SLL include BTKi and venetoclax with or without rituximab. Allo-HSCT is rarely used in patients with CLL/SLL, except among select patients with refractory CLL/SLL with del(17p) who are young, fit, and have matched donors.¹

Both ibrutinib and acalabrutinib are indicated in adult patients with R/R CLL/SLL and zanubrutinib is currently being reviewed by the FDA for a CLL/SLL indication.⁴⁻⁶ Several studies have investigated the safety and efficacy of BTKis in patients with R/R CLL/SLL,

including ELEVATE-RR (NCT02477696) and ALPINE (NCT03734016).^{18,19}

ELEVATE-RR Clinical Trial

The phase 3 noninferiority ELEVATE-RR clinical trial randomized patients with R/R CLL harboring del(17p) or del(11q) to receive acalabrutinib (n = 268) or ibrutinib (n = 265). The primary end point was noninferiority based on IRC-assessed PFS. Hierarchical secondary end points, which were only studied if the primary end point was met, included OS, incidence of any-grade atrial fibrillation or flutter, grade 3 or higher infection, and Richter transformation.¹⁸

At the median duration of follow-up of 41.1 months in the acalabrutinib arm and 40.7 months in the ibrutinib arm, the median IRC-assessed PFS was 38.4 months in both arms.¹⁸

Acalabrutinib, when with ibrutinib, had lower incidences of atrial fibrillation or flutter (9.4% vs 16.0%), bleeding (38.0% vs 51.3%), hypertension (9.4% vs 23.2%), interstitial lung disease or pneumonitis (2.6% vs 6.5%), diarrhea (34.6% vs 46.0%), arthralgia (15.8% vs 22.8%), and contusion (11.7% vs 18.3%).¹⁸

ALPINE Clinical Trial

The phase 3 ALPINE clinical trial randomized patients with R/R CLL/SLL to receive zanubrutinib or ibrutinib. Investigator-determined ORR was the primary end point, with a hierarchical testing approach used to test the superiority of zanubrutinib, if it was found to be noninferior to ibrutinib.¹⁹

A preplanned interim analysis of the first 415 randomized patients showed that at a median follow-up of 15 months, the ORR was significantly higher with zanubrutinib than with ibrutinib (78.3% vs 62.5%). Among patients with del(11q) and del(17p), the ORR was 83.6% for patients treated with zanubrutinib vs 69.1% for patients treated with ibrutinib. Zanubrutinib was also associated with higher rates of 12-month PFS (94.9% vs 84.0%) and OS (97.0% vs 92.7%) as well as lower rates

of atrial fibrillation or flutter (2.5% vs 10.1%), major bleeding (2.9% vs 3.9%), and AEs leading to discontinuation (7.8% vs 13.0%) or death (3.9% vs 5.8%).¹⁹ A summary of rates of the most frequent AEs of any grade that occurred in more than 10% of patients in the safety population is shown in the **FIGURE**.¹⁹

The authors concluded that the more selective inhibition as well as complete and sustained occupancy of BTK may lead to better efficacy and safety with zanubrutinib.¹⁹

STAKEHOLDER INSIGHTS

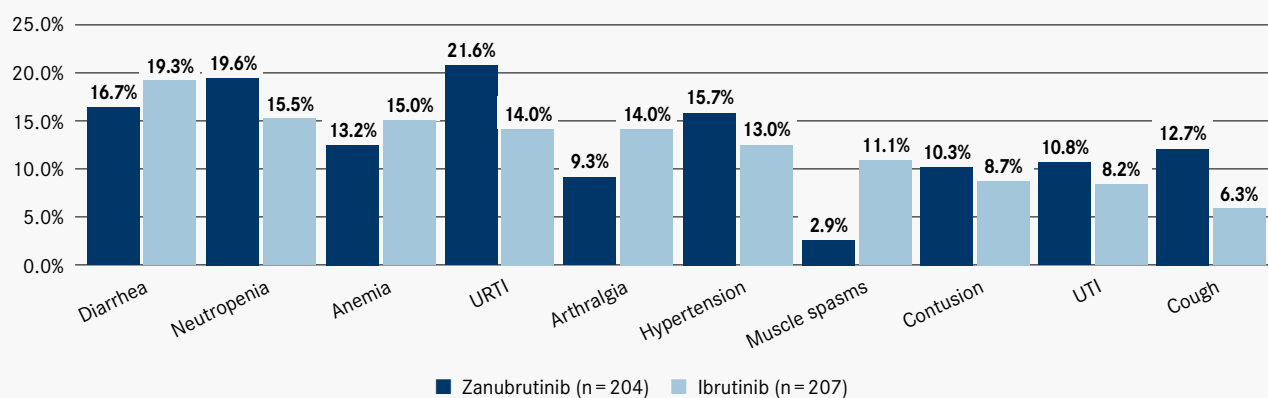
Selection of therapy depends on therapy received in the frontline setting. One panelist suggested venetoclax-based therapies for patients who previously received chemoimmunotherapy and switching from one BTKi to another for patients who previously received a BTKi. The panelist said retreatment with the same BTKi could be considered for patients who achieved remission and then progressed while off therapy.

The panelists said they were already starting patients with acalabrutinib rather than ibrutinib in clinical practice prior to the publication of the ELEVATE-RR trial results, which provided additional evidence that acalabrutinib was better tolerated than ibrutinib. If zanubrutinib is approved for a CLL/SLL indication, many of the panelists said that they would consider it as their second choice behind acalabrutinib, primarily because they have more experience using acalabrutinib.

NOVEL NONCOVALENT BTKIS

Cys481 and *PLCG2*, immediately downstream of BTK, are commonly observed acquired resistance mutations in patients with CLL/SLL who take ibrutinib or acalabrutinib.²⁰

FIGURE.
MOST FREQUENT ALL-GRADE AES IN > 10.0% PATIENTS WITH CLL/SLL IN THE ALPINE CLINICAL TRIAL^{19,a}



AE, adverse events; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; URTI, upper respiratory tract infection; UTI, urinary tract infection.

^aSafety analysis population only.

These mutations can be detected several months prior to clinical progression and occur relatively consistently across frontline and R/R settings, as well as in patients who switched to acalabrutinib after intolerance to ibrutinib.^{21,22}

Some experts have suggested that the covalent BTKis may incompletely inhibit BTK toward the end of the dosing interval, which contributes to resistance and prompts the need for novel BTKis that overcome common resistance mechanisms.²³

Pirtobrutinib

Pirtobrutinib (LOXO-305) is a reversible, investigative BTKi that potently and selectively inhibits wild-type and C481S-mutated BTK. The phase 1/2 BRUIN trial (NCT03740529) studied pirtobrutinib in 323 patients with mature B-cell malignancies. Of these patients, 170 had CLL/SLL and received a median of 3 prior therapies. The recommended phase 2 dose was 200 mg per day. No dose-limiting toxicities were observed.²³

Neutropenia was the most common grade 3 or higher AE that occurred in at least 10.0% of all patients; the majority of AEs, however, were grade 1 or 2.

Atrial fibrillation or flutter was reported in 2 of 323 patients in the overall safety population and was considered unrelated to pirtobrutinib.²³

The ORR was 63.0% among 139 patients with CLL/SLL who were evaluable for efficacy and 62.0% among 121 patients with CLL/SLL previously treated with BTKi. Among the patients who previously received a BTKi and had *BTK* C481S-mutated disease, the ORR was 75.0% (15 of 20). The ORR was 60.0% (18 of 30) in patients without these mutations, 67.0% (53 of 79) in patients who discontinued a covalent BTKi because of disease progression, and 52.0% (22 of 42) who discontinued a covalent BTKi because of toxicity or another reason.²³

The authors concluded that pirtobrutinib was well tolerated with a wide therapeutic index and activity across a heterogeneous population, although extended follow-up on response duration is needed given the long natural history of CLL.²³

ARQ-531

ARQ-531 is a potent, reversible inhibitor of wild-type and C481S-mutant BTK that showed superiority over ibrutinib in CLL mouse models.²⁴

A phase 1 dose-escalation study (NCT03162536) included patients with selected hematologic malignancies. The results showed that 4 of 6 patients with BTK C481S-mutated CLL who received a 65-mg starting dose had a partial response. AEs occurred in 18 of 34 patients (52.9%); the most commonly reported AEs were nausea, diarrhea, decreased neutrophil count, and fatigue. The authors noted that the “robust antitumor activity” in heavily pretreated, *BTK* C481S-mutated CLL warrants further study.²⁴

STAKEHOLDER INSIGHTS

Pirtobrutinib and ARQ-531 have promising efficacy for patients who have BTKi resistance mutations or progressed on covalent BTKi-based regimens. The experts observed that pirtobrutinib is generally better tolerated than ARQ-531, which may be particularly relevant when considering the need for long-term dosing. Long-term follow-up data are important to assess DOR, types of mutations that occur after progression, and potential salvage therapies. If these reversible BTKis

are approved, the panel said that they are likely to be used following treatment with first- and second-generation BTKis.

The stakeholders concluded the discussion by noting that while the recent progress in treatment of CLL/SLL with BTKis has been impressive, key areas of research moving forward include defining optimal time-limited therapies that are adapted for minimal residual disease status, identifying potentially curative therapies for CLL/SLL, and developing therapies that minimize AEs and maximize QOL. They also noted the importance of educating colleagues in community practice about the new therapies for CLL/SLL. ■

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**ANTHONY MATO,
MD, MSCE**

Director, Chronic Lymphocytic
Leukemia Program
Memorial Sloan Kettering
Cancer Center
New York City, New York

INTRODUCTION

Editors from *OncoLive*[®] spoke with hematologic malignancy expert Anthony Mato, MD, MSCE, for his insights on recent advancements in the treatment of chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), unmet therapeutic needs, the potential role of chimeric antigen receptor (CAR) T-cell therapy, and data from clinical studies of interest to be presented at the 2021 American Society of Hematology (ASH) Annual Meeting on December 11-14, 2021.

**Interview transcripts are slightly edited for readability.*

➤ TO SEE THE FULL VIDEO INTERVIEW, VISIT [ONCLIVE.COM](https://www.onclive.com)

The Evolving Therapeutic Landscape for CLL/SLL: Expert Perspectives

OncoLive[®]: What are the most important advances you have seen in recent years in the treatment of patients with CLL/SLL?

ANTHONY MATO, MD, MSCE: Over the past couple of years, there has been a tremendous explosion of progress in the field. We've had long-term follow-up data from the original drugs that were approved, like ibrutinib and venetoclax. We've had newer drugs come onto the scene, particularly the covalent and more selective Bruton tyrosine kinase inhibitors [BTKis] like acalabrutinib. We've seen the development of noncovalent BTKis like pirtobrutinib, which have really demonstrated incredible activity.

We've had updates on CAR T-cell therapies and how they may fit into the landscape. Of course, a general theme in oncology is that once you have several active drugs, we learn how to put them together in combinations, and we're starting to see intriguing data in terms of tolerability and depth of remission for novel doublet and triplet combinations.

OncoLive[®]: What unmet needs still remain for the treatment of patients with CLL/SLL and what questions remain to be addressed in future studies?

MATO: Now we're seeing patients who are sequencing through multiple lines of therapy.

An unmet need is for treatments for patients who were exposed to or are refractory to one or more novel agents.

We're trying to learn about mechanisms of resistance to these drugs to decide what would fit next into this space, whether currently approved drugs are a good fit, whether we need to develop new classes of agents, and how to compare those agents to current standards of care in order to move the field forward.

OncoLive[®]: Where do you foresee CAR T-cell therapy fitting into the treatment paradigm?

MATO: Right now, I think CAR T-cell therapies are an important proof of concept in terms of immunotherapy for CLL, taking the baton from where allogeneic stem cell transplantation was a few years ago.

The major question I have is that when you have agents such as BTKis, venetoclax, and even noncovalent BTKis, how does sequencing justify the use of CAR T-cell therapies prior to those drugs? Right now I think CAR T-cell therapy is still for a later line of therapy, maybe a third-line therapy, for patients who have been at least through 2 or 3 classes of prior agents. Maybe that will change, but I think the issue at the heart of all this is to design studies that

“Now we’re seeing patients who are sequencing through multiple lines of therapy. An unmet need is for treatments for patients who were exposed to or are refractory to one or more novel agents. We’re trying to learn about the mechanisms of resistance to these drugs to decide what would fit next into this space, whether currently approved drugs are a good fit, whether we need to develop new agents, and how to compare those agents to current standards of care in order to move the field forward.”

determine which patients would be the best fit for CAR T-cell therapy in earlier lines of treatment and how to prove that the patient benefited from that more intensive therapy as opposed to sequencing through multiple targeted therapies.

OncLive®: What ongoing clinical trials are of interest to you, and what data are you hoping to see presented at ASH this year?

ANTHONY MATO, MD, MSCE: What I’m hoping to see are updated data on the bispecifics. I think that is an interesting class. [I am also hoping to see] updated data on the noncovalent BTKis.

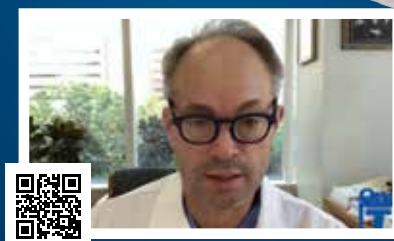
I don’t know whether or not we’ll see zanubrutinib data in

the frontline readout from the randomized perspective. We’ve seen a snippet of data from the comparison of the covalent BTKis, ibrutinib vs acalabrutinib comparison [data], and ibrutinib vs zanubrutinib data. It is probably too soon for an update, but if there were new data, I would be interested.

Of course, there are so many new classes [of drugs] in development. [The studies of these agents] may not be in oral presentations, but the poster sections are where there is activity for newer agents.

I’m excited about ASH, but it’s not entirely clear to me what will be the next big readout at the meeting. I think this year may be more about some of the smaller trials. Next year, we’ll have data from some of the bigger randomized trials. ■

To hear more about **Chronic Lymphocytic Leukemia** from these experts and others, visit **OncLive.com**.



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