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MANTLE CELL LYMPHOMA  
CHRONIC LYMPHOCYTIC LEUKEMIA

DECEMBER 11, 2022

VIRTUAL WORKSHOP

# SCIENTIFIC INTERCHANGE & WORKSHOP

Bruton Tyrosine Kinase (BTK)  
Inhibitors in **Mantle Cell  
Lymphoma** and **Chronic  
Lymphocytic Leukemia**



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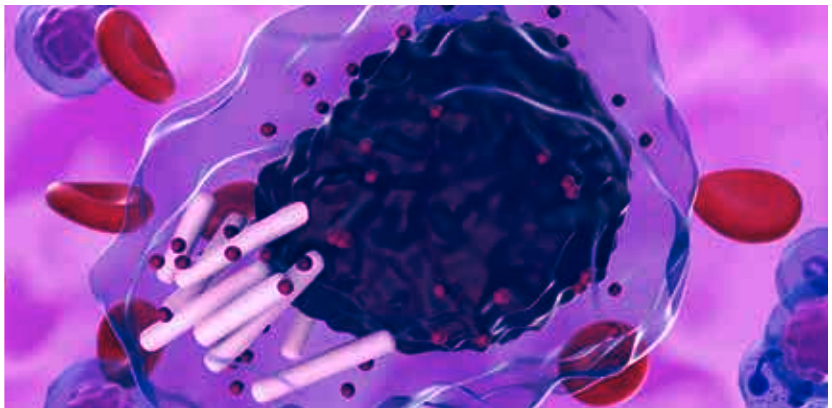
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## MCL/CLL



## KEY TAKEAWAYS

- ▶ In relapsed or refractory (R/R) mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL), second-generation Bruton tyrosine kinase inhibitors (BTKis) have become a preferred treatment approach for the majority of patients, with selection of BTKi dependent upon patient-specific factors and individual BTKi adverse event (AE) profiles.
- ▶ Venetoclax offers a bridging therapy for patients with MCL who experience disease progression on a BTKi overlap; however, due to less durable responses than those seen with treatment of CLL, utility is limited to short-term treatment of MCL.
- ▶ In patients with MCL, the noncovalent BTK inhibitor pirtobrutinib may offer a continuous therapy option for some patients or serve as a bridging therapy in patients who are candidates for chimeric antigen receptor (CAR) T-cell therapy.
- ▶ Pirtobrutinib activity is not dependent upon the C481 binding site of BTK; this highlights the possibility of its use in an associated role in CLL that is refractory to covalent BTKis or as a doublet therapy option with venetoclax in patients with CLL who experience progression on zanubrutinib.
- ▶ In MCL, the CD20-directed bispecific monoclonal antibody (mAb) glofitamab offers an off-the-shelf treatment option with fewer logistical challenges than those associated with some CAR T-cell therapies.
- ▶ As an emerging treatment option, BTK degraders (eg, NX-2127) represent a novel strategy to overcome treatment resistance with BTKis, including triple-refractory disease; these agents also offer an alternative treatment option for patients with MCL, who are generally older, more frail, or poor candidates for CAR T-cell therapy.
- ▶ Measurable residual disease (MRD) testing may be helpful for prognostic and counseling services or as an indicator for discontinuing therapy. However, utility is limited for treatment decision-making; MRD testing should be used with caution, especially in patients with high-risk disease or Richter transformation.

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# Bruton Tyrosine Kinase (BTK) Inhibitors in Mantle Cell Lymphoma and Chronic Lymphocytic Leukemia

## INTRODUCTION

**ON DECEMBER 11, 2022**, a select group of hematologic oncologists participated in a virtual workshop to discuss the role of BTKis in the treatment of MCL and CLL. **Lindsey Roeker, MD**; and **Alexey Danilov, MD, PhD**; led an expert discussion regarding perspectives and insights on the available evidence around using BTKis in MCL and CLL, novel treatment approaches, and optimal management strategies for combining and sequencing therapies.

## BTK INHIBITORS IN MCL

MCL is a rare and aggressive B-cell malignancy accounting for approximately 3% of all non-Hodgkin lymphomas diagnosed in men and women in the United States.<sup>1,2</sup> There have been advances in treatment over the last few decades, yet MCL-associated survival rates have remained low relative to those of other B-cell lymphoma subtypes.<sup>1-3</sup> Patients with advanced age, comorbidities, or other frailties are often unable to tolerate intensive therapies that result in longer intervals of progression-free survival (PFS).<sup>3,4</sup> BTKis offer an alternative treatment approach with improved survival benefits in this patient population.<sup>3</sup>

## PREVIOUSLY UNTREATED MCL

Guidelines from the National Comprehensive Cancer Network (NCCN) base treatment selection for previously untreated MCL on eligibility for high-dose therapy with autologous stem cell transplant (ASCT), the presence of *TP53* mutations, and other patient-specific clinical

factors.<sup>5</sup> Currently, the preferred induction therapies for both patients who intend to receive ASCT and those with no intention of receiving ASCT include various multiagent chemotherapy regimens. Survival benefits associated with the addition of BTKis in patients with previously untreated MCL have been evaluated in several clinical trials, including the TRIANGLE (NCT02858258), SHINE (NCT01776840), and ECHO (NCT02717624) studies.<sup>6-9</sup>

### TRIANGLE Study

The phase 3 TRIANGLE study evaluated the addition of ibrutinib to standard induction chemotherapy that includes the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) regimen alternating with the R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) regimen and 2 years of maintenance ibrutinib with ASCT (arm A+I) or without ASCT (arm I) compared with standard treatment (R-CHOP/R-DHAP followed by ASCT) (arm A) in 870 patients 65 years or younger with previously untreated, advanced stage II to IV MCL.<sup>6</sup>

The overall response rate (ORR) and complete response (CR) rates in arm A were 94% and 36%, respectively, compared with 98% and 45% in the combined A+I/I groups. Three-year failure-free survival (FFS) and overall survival (OS) were also higher among the A+I group compared with patients in group A (FFS, 88% vs 72%, respectively; HR, 0.52;  $P = .0008$ ) (OS, 91% vs 86%). During the induction phase, AEs of grade 3 or greater did not differ substantially between treatment groups; however, during the

maintenance phase, a higher number were reported in the ibrutinib group.<sup>6</sup>

### SHINE Study

The phase 3 SHINE study included 523 patients 65 years or older with previously untreated MCL.<sup>7,8</sup> Patients received ibrutinib or placebo, both in combination with BR (bendamustine plus rituximab). In the maintenance phase, rituximab was added to either BR or placebo in patients who achieved a CR or partial response (PR). Median PFS was 80.6 months in the ibrutinib group and 52.9 months in the placebo group, and the reported CR rate was higher among patients in the ibrutinib group than those in the placebo arm (65.5% vs 57.6%, respectively). There was no difference in OS between treatment groups ( $P = .648$ ). Grade 3 or 4 treatment-emergent AEs (TEAEs) occurred in 81.5% of patients in the ibrutinib group and 77.3% of those in the placebo group. Atrial fibrillation occurred more frequently among patients in the ibrutinib group (13.9% vs 6.5%); however, observed rates of major hemorrhage and hypertension were similar between treatment groups.<sup>7,8</sup>

### ECHO Study

The phase 1b ECHO study investigated acalabrutinib in combination with venetoclax and rituximab in patients ( $N = 21$ ) with previously untreated MCL.<sup>9</sup> The ORR was 100%, with a CR rate of 90% and a PR rate of 10% as assessed by PET/CT. At 24 months, the PFS rate was 54%, and the OS rate was 75%. AEs of at least grade 3 were reported in 57.1% patients, with the most common being neutropenia (33.3%) and pneumonia (14.3%).

## STAKEHOLDER INSIGHTS

**Tyrel Phillips, MD**, noted that the TRIANGLE study data highlight the benefits of adding a BTKi to the standard of care induction therapy or as an alternative to ASCT for younger patients with previously untreated MCL. There are fewer good quality data supporting second-generation BTKis such as acalabrutinib and zanubrutinib in this treatment setting; however, **Carolyn Owen, MD**, noted that it may be reasonable to use a second-generation BTKi in place of ibrutinib when following a TRIANGLE study-based treatment approach due to the lower associated toxicity and discontinuation rates. **Matthew Davids, MD, MMSc**, added that results from the ECHO study should offer clarity regarding this treatment approach in older patients. Faculty indicated that superiority or noninferiority studies comparing ibrutinib with second-generation BTKis in MCL may also be helpful.

Treatment for patients with MCL and *TP53* mutations typically includes a low-intensity induction regimen (eg, rituximab monotherapy, BR, BR alternating with the high-dose CR [cytarabine plus rituximab]) followed by BTKi off-label, with a primary goal of minimizing treatment-associated toxicity to allow for future CAR-T therapy.

**Dipenkumar Modi, MD**, emphasized the importance of histology regarding treatment choice. For classic subtypes, BR alternating with CR or other regimens is a reasonable approach. However, in cases with pleomorphic or blastoid histology, BR is insufficient, and the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and

dexamethasone plus methotrexate and cytarabine) regimen or R-CHOP alternating with DHAP would be more appropriate.

For most patients 65 years or older, the first-line treatment approach for MCL typically includes BR; however, faculty noted that treatment selection often depends upon patient-specific factors. In patients with chronic kidney disease and other comorbidities, **Pallawi Torka, MD**, often opts for BTKi monotherapy. However, **Ian Flinn, MD, PhD**, noted that the R<sup>2</sup> (lenalidomide plus rituximab) regimen is another option for patients unable to tolerate full-dose bendamustine, and it may be more readily approved with some third parties. **John Allan, MD**, commented that the VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen is also a viable option in patients with renal failure. **Danilov** added that he also has used VR-CAP in patients who develop a rash with bendamustine. Experts also noted a role for RBAC500 (rituximab, bendamustine, cytarabine) in patients with high-risk features (eg, blastoid or pleomorphic histology; *TP53* mutations) or borderline age ( $\geq 72$  years), noting that it involves use of a shorter regimen that is generally tolerated by most patients and allows for transplant if desired.

## BTK INHIBITORS IN R/R MCL

Preferred treatment approaches in patients with R/R MCL generally include a BTKi-based regimen.<sup>5</sup> Covalent BTKis with FDA-approved indications in this treatment setting include the first-generation BTKi ibrutinib and 2 second-generation BTKis, acalabrutinib and zanubrutinib.<sup>10-12</sup> Ibrutinib was initially approved for R/R MCL based on

results of the open-label PCYC-1104-CA study (NCT01236391), which included 111 previously treated patients.<sup>13</sup> The ORR was 68%, with 21% of patients achieving a CR and 47% of patients achieving a PR. The estimated median duration of response (DOR) was 17.5 months, and the median PFS was 13.9 months. The median OS was not reached. Due to off-target AEs (eg, atrial fibrillation, hypertension, hemorrhage) observed with ibrutinib, second-generation inhibitors were developed with greater selectivity to minimize off-target drug-associated AEs.<sup>14,15</sup>

A summary of long-term efficacy and safety data is shown in **TABLE 1**.<sup>16-19</sup> Current NCCN recommendations for R/R MCL include continuous acalabrutinib or zanubrutinib as well as the R<sup>2</sup> regimen. Several BTKi-related combinations are also being studied for the management of R/R MCL; these include, but are not limited to, ibrutinib plus bendamustine, ibrutinib plus obinutuzumab with or without venetoclax, acalabrutinib plus bendamustine and rituximab, zanubrutinib plus rituximab, and zanubrutinib combined with venetoclax, obinutuzumab, ibrutinib, and rituximab.

## NONCOVALENT BTK INHIBITORS IN MCL

The phase 1/2 BRUIN trial (NCT03740529) evaluated the safety and efficacy of pirtobrutinib in 90 patients with previously treated MCL.<sup>20</sup> Updated safety and efficacy data presented at the 2022 American Society of Hematology (ASH) Annual Meeting and Exposition (ASH 2022) demonstrated continued favorable response rates among patients with MCL (ORR, 58%), including in those with high-risk histologies (ORR: blastoid, 75%; pleomorphic, 50%). Overall, pirtobrutinib was well-tolerated, with low rates of grade 3 or greater TEAEs (hypertension, 3%; hemorrhage, 2%; atrial fibrillation, 1%).<sup>20</sup> The NCCN

**TABLE 1.**  
LONG-TERM SAFETY AND EFFICACY DATA FOR BTKIS IN R/R MCL<sup>16-19</sup>

BTKi Trial name (NCT number)	ORR	mPFS	mOS	mDOR	Safety
<b>Ibrutinib<sup>a</sup></b> PCYC-1104-CA (NCT01236391), RAY (NCT01646021), and SPARK (NCT01599949) trials	69.7%	12.5 mo	26.7 mo	21.8 mo	TEAEs of interest (G ≥ 3): NP, 17.0% AFib, 6.8% HTN, 5.1%
<b>Acalabrutinib<sup>b</sup></b> ACE-LY-004 (NCT02213926)	81.0%	22.0 mo	59.2 mo	29.0 mo	TEAEs (AG/G ≥ 3): INF, 67.7%/16.9% AFib, 2.4%/0% HTN, 4.0%/1.6% HEM, 37.1%/4.0%
<b>Zanubrutinib<sup>c</sup></b> (NCT03206970)	83.7%	33.0 mo	NR (36.0-mo est, 74.8%)	NR	TEAEs (AG/G ≥ 3): NP, 50.0%/19.8% INF, 65.1%/18.6% AFib, NR HTN, 10.3%/2.9% HEM, 36.0%/3.5%

AFib, atrial fibrillation; AG, all grades; BTKi, Bruton tyrosine kinase inhibitor; est, estimate; G, grade; HEM, hemorrhage; HTN, hypertension; INF, infection; MCL, mantle cell lymphoma; mDOR, median duration of response; mo, month(s); mOS, median overall survival; mPFS, median progression-free survival; NCT, National Clinical Trial; NP, neutropenia; NR, not reached; ORR, overall response rate; R/R, relapsed/refractory; TEAEs, treatment-emergent adverse effects; y, year(s).

<sup>a</sup>7.5-y follow-up of pooled data

<sup>b</sup>Median follow-up of 3.5 y

<sup>c</sup>Median follow-up of 35 mo

guidelines recommend treatment with pirtobrutinib for R/R MCL in the third-line setting and beyond.<sup>5</sup>

The ongoing, randomized, open-label phase 3 BRUIN-MCL-321 trial (NCT04662255) is evaluating pirtobrutinib monotherapy versus investigator’s choice of covalent BTKi monotherapy with ibrutinib, acalabrutinib, or zanubrutinib in patients with previously treated, BTKi-naive MCL.<sup>21</sup> Patients with a history of current or prior central nervous system (CNS) disease, significant cardiovascular disease, stroke, or intracranial hemorrhage within 6 months of treatment initiation or those who received ASCT or CAR T-cell therapy within 60 days of randomization are excluded from the study. The primary end point for the study is PFS by Independent Review Committee. Key secondary end points include ORR, DOR, OS, safety, and patient reported outcomes.<sup>21</sup>

### STAKEHOLDER INSIGHTS

In the R/R MCL treatment setting, faculty typically opt for BTKi-based regimens with a preference for second-generation BTKis due to better tolerability in most patients. Treatment can depend on third-party coverage, but **Flinn** expressed that patient-specific factors and AE profiles can also impact the choice of BTKi. He noted that in patients with certain cardiovascular comorbidities (eg, hypertension), acalabrutinib may be preferred over zanubrutinib.

Experts also expressed a continued role for ibrutinib in MCL, with **Owen** noting fewer challenges in practice with toxicity and intolerance associated with ibrutinib in MCL vs CLL treatment settings. **Phillips** agreed, noting that shorter

survival rates generally associated with MCL may contribute to this observed difference.

Some faculty are using venetoclax as a bridging therapy in patients who progress on a BTKi overlap, but they pointed out that the utility of venetoclax in MCL is somewhat limited compared with CLL. Responses with venetoclax are generally not durable in patients with MCL, which limits use to short-term treatment strategies in this setting.

Regarding the potential role of pirtobrutinib in MCL, **Flinn** noted that there are a lot of factors to consider. Depending on the age of the patient and their fitness, pirtobrutinib may be used as a continuous therapy or as a bridge therapy for patients eligible for CAR T-cell therapy.

There were differing opinions regarding whether pirtobrutinib

should be moved to earlier lines of treatment. **Dauids** believes that pirtobrutinib would be beneficial in the earlier treatment setting. **Modi** agreed, further noting that ongoing trials will provide clarity on the matter. **Torka** and **Phillips** expressed reservations and noted a need for more data. **Phillips** also cautioned that if pirtobrutinib is moved to earlier lines, it could further limit available salvage therapy options.

## EMERGING TREATMENT STRATEGIES IN MCL

### *Glofitamab*

Glofitamab is a novel 2:1 CD20×CD3 T-cell engaging bispecific antibody, allowing for bivalent affinity for CD20 on B cells and monovalent activity towards CD3 on T cells.<sup>22</sup> Early results from a phase 1/2 trial (NCT03075696) investigating glofitamab in 37 patients with R/R MCL demonstrated an ORR of 83.8%, with a CR observed in 73.0% of patients and a median DOR of 12.6 months.<sup>22</sup> The most frequently reported AEs were cytokine release syndrome (CRS; 75.7%) and neutropenia (40.5%). CRS events were all manageable, with 17 patients requiring tocilizumab. Neurologic AEs were reported in 51.4% of patients (grade 1/2, 18 patients; grade 3, 1 patient). No patients required treatment discontinuation secondary to AEs.<sup>22</sup>

### *NX-2127*

The mechanism of action associated with NX-2127, a BTK degrader, involves IKZF3 targeting for ubiquitination and subsequent proteasome-mediated degradation; it represents a potential mechanism to overcome treatment resistance associated with BTK and BCL2 inhibitors.<sup>23</sup> The phase 1 NX-2127-001 trial (NCT04830137) is evaluating NX-2127 in patients with R/R CLL and other B-cell malignancies, including MCL. Early data from the study, based on 12 response-evaluable patients with CLL, showed an ORR of

33%, with an increasing trend upon longer follow-up and responses noted in BTKi/BCL2 double-refractory patients who progressed on a noncovalent BTKi.<sup>23,24</sup> The most commonly reported TEAEs included fatigue (any grade, 62%; grade ≥ 3, 0%), neutrophil decrease (any grade, 39%; grade ≥ 3, 35%), and anemia (any grade, 27%; grade ≥ 3, 15%).<sup>23</sup>

## STAKEHOLDER INSIGHTS

**Torka** indicated enthusiasm regarding glofitamab, noting that it could offer an off-the-shelf option with fewer logistical challenges than those related to CAR T-cell therapies. There is a lot of momentum behind CAR T-cell therapies, but **Torka** believes that bispecific antibodies will have a growing role in the community setting. **Flinn** agreed that the glofitamab data are encouraging, but he noted that it is unlikely that it will be curative for most patients. He believes patients will use a bispecific antibody followed by CAR T-cell therapy upon progression.

**Owen** expressed excitement regarding the BTK degrader (NX-2127) concept as a potential strategy to overcome treatment resistance with BTKis. It would offer another oral option for patients with MCL who are older and more frail, and, therefore, poor candidates for CAR T-cell therapy. **Danilov** indicated a role for BTK degraders in patients with triple-resistant disease who progress following treatment with ibrutinib, venetoclax, and pirtobrutinib. **Flinn** added that lisocabtagene maraleucel (liso-cel), a CAR T-cell therapy, has shown promising results with lower toxicity, so it might be an option for frail patients. On the other hand, it has higher levels of neurologic toxicity in patients

with MCL and presents greater access problems.

## BTK INHIBITORS IN CLL

Treatment of CLL in the first-line setting depends upon disease- and patient-specific factors and the presence of certain genetic alterations, including deletion of the short arm of chromosome 17 (del[17p]) and *TP53* mutations.<sup>25</sup> Based on trial data from ELEVATE-TN (NCT02475681), RESONATE-2 (NCT01724346), Alliance A041202 (NCT01886872) SEQUOIA (NCT03336333), and CLL 14 (NCT02242942), preferred regimens include combination regimens (acalabrutinib with or without obinutuzumab or venetoclax plus obinutuzumab) or monotherapeutic approaches (ibrutinib or zanubrutinib).

Other recommended regimens for patients 65 years or older or for those with significant comorbidities include bendamustine plus rituximab or obinutuzumab, and chlorambucil with obinutuzumab. Due to low response rates, chemoimmunotherapeutic options are not recommended in patients with del(17p) or *TP53* mutations.<sup>25</sup> **TABLE 2** offers long-term follow-up data from research on the frontline treatment of CLL.<sup>26-33</sup>

## STAKEHOLDER INSIGHTS

The faculty noted a shift in treatment practices, with acalabrutinib replacing ibrutinib in the first-line treatment setting for CLL. Generally, BTKis are the preferred treatment approach for patients with del(17p) or *TP53* mutations. For young patients with bulky tumors and del(17p) or deletions in the long arm of chromosome 11 (del[11q]), some faculty noted a preference for ibrutinib with venetoclax followed by ibrutinib maintenance. Some noted that according to the results from the GLOW study (NCT03462719), in patients with

lower-risk disease (eg, *IGHV*-mutated, MRD-positive disease), it may be appropriate to stop therapy once the MRD is low. For these patients, first-line therapy is often their best chance for a fixed-duration regimen; however, patients with high-risk disease may benefit from continued venetoclax use.

Allan highlighted the value of a

shared decision-making process, explaining that he will have an in-depth discussion with patients about the benefits and limitations of using a second-generation BTKi or venetoclax/obinutuzumab. For patients needing a quick response, the addition of an anti-CD20 mAb to BTKi therapy may be appropriate; for other patients, clinical trials may be an option.

**Praveen Ramakrishnan, MD, MS**, emphasized the importance of disease- and patient-specific factors. In addition to the presence of high-risk disease factors (eg, del[17p], *TP53* mutations), comorbidities are important considerations. Patients with cardiovascular comorbidities or those receiving anticoagulation therapy are poor candidates for

**TABLE 2.** SUMMARY OF LONG-TERM FOLLOW-UP TRIAL DATA FOR FIRST-LINE TREATMENT OF CLL<sup>26-33</sup>

Trial name (NCT number)	Intervention	Population	Efficacy	Safety <sup>a</sup>
RESONATE-2 (NCT01724346)	IBR vs CLB	TN CLL (N = 269; mFU, 7.4 y)	<i>IBR vs CLB</i> ORR: 92.0% vs 37.0% PFS (84.0-mo est): 59.0% vs 9.0%	TEAEs of interest (AG/G ≥ 3): AFib: 7.0%/6.0% HTN: 25.0%/12.0%
Alliance A041202 (NCT01886872)	BR vs IBR vs IBR+R	High-risk TN CLL (N = 547; mFU, 55.0 mo)	<i>BR vs IBR vs IBR+R</i> PFS (48.0-mo est): 47% vs 76.0% v. 76.0% OS (48.0-mo est): 84.0% vs 85.0% vs 86.0%	TEAEs of interest (AG): AFib: 19.0% HTN: 73.0%
ELEVATE-TN (NCT02475681)	ACALA+OBI vs ACALA vs OBI+CLB	TN CLL (N = 535; mFU, 58.2 mo)	<i>ACALA+OBI vs ACALA vs OBI+CLB</i> ORR: 96.0% vs 90.0% vs 83.0% PFS (60.0-mo est): 84.0% vs 72.0% vs 20.0% OS (60.0-mo est): 90.0% vs 84.0% vs 82.0%	AFib (AG/G ≥ 3): ACALA+OBI, 6.2%/1.1% ACALA, 7.3%/1.1% HTN (AG/G ≥ 3): ACALA+OBI, 9.6%/4.5% ACALA, 8.9%/3.9%
SEQUOIA (NCT03336333)	ZANU vs BR	TN CLL (N = 590; mFU, 26.2 mo)	<i>ZANU vs BR</i> ORR by IRC: 94.6% vs 85.3% PFS (24.0-mo est): 85.5% vs 69.5% OS (24.0-mo est): 94.3% vs 94.6%	TEAEs of interest (AG): AFib: 3.0% Major bleeding: 5.0%
CLL14 (NCT02242942)	VENE+OBI vs OBI+CLB	TN CLL (N = 432; mFU, 65.4 mo)	<i>VENE+OBI vs OBI+CLB</i> PFS (60.0-mo est): 62.6% vs 27.0% OS (60.0-mo est): 81.9% vs 77.0%	Most common TEAEs (AG/G3/G4): NP: 5.0%/25.0%/28.0% IRR: 36.0%/8.0%/1.0% TCP: 10.0%/9.0%/4.0%
CAPTIVATE (NCT02910583)	IBR+VENE vs PBO	TN CLL (N = 164; mFU, 56.0 mo)	<i>IBR+VENE vs PBO</i> PFS: 95.0% vs 88.0% OS: 98.0% vs 100.0%	TEAEs of interest: AFib (AG): 5.0% HTN (AG): 16.0%
Phase 2 study (NCT02427451)	IBR+VENE+OBI	TN or R/R CLL (N = 75; mFU, 57.0 mo)	<i>TN vs R/R CLL</i> PFS (48.0-mo est): 96.0% vs 96.0% OS (48.0-mo est): 85.0% vs 100.0%	TEAEs of interest (AG/G3): NP: 95.0%/73.0% TCP: 91.0%/28.0% HTN: 85.0%/39.0% AFib: 11.0%

ACALA, acalabrutinib; AFib, atrial fibrillation; AG, all grades; BR, bendamustine/rituximab; CLB, chlorambucil; CLL, chronic lymphocytic leukemia; est, estimate; G, grade; G3/G4, grade 3/grade 4; HEM, major hemorrhage; HTN, hypertension; IBR, ibrutinib; INF, infection; IRC, Independent Review Committee; IRR, infusion-related reaction; mFU, median follow-up; mo, month(s); NCT, National Clinical Trial; NP, neutropenia; NR, not reached; OBI, obinutuzumab; ORR, overall response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; R, rituximab; R/R, relapsed/refractory; TCP, thrombocytopenia; TEAEs, treatment-emergent adverse effects; TN, treatment naïve; VENE, venetoclax; ZANU, zanubrutinib.

<sup>a</sup>Results reported for study treatment arm(s)

BTKi therapy; further, venetoclax may not be appropriate for those at risk for tumor lysis syndrome (TLS) or with poor kidney function.

**Krish Patel, MD**, expressed that patient preference is a big decision-driver, with some patients having the motivation to receive more intensive fixed-duration therapy and others preferring to take the oral medication and avoid multiple trips to the infusion center. **Modi** added that frequent follow-up visits for TLS monitoring or other laboratory work required with certain regimens frequently impact the treatment decision. Generally, patients are in the best position for venetoclax in the first-line setting, because they are younger and more fit. **Owen** further noted that venetoclax/obinutuzumab ramp-up in the first-line setting is less challenging than is venetoclax/rituximab in the second-line setting.

**Patel** noted that MRD test results are useful for prognostic and counseling purposes. He added that routine MRD testing is done every 6 months at his site, and it has been used as an indicator to stop therapy at 9 months in patients with MRD-negative disease and persistent neutropenia. **Craig Portell, MD**, also believes there is value in MRD tracking. He has not seen an MRD conversion; however, MRD tracking can be helpful in detecting noncompliance and guiding treatment decisions, such as reinitiating BTKi therapy. **Allan** added that it can also be helpful if a transplant is being considered.

### R/R CLL

Second-line treatment selection for R/R CLL is generally guided by specific clinical considerations, including prior first-line therapy, duration of remission, and the presence of acquired resistance to

treatment.<sup>25</sup> Based on results reported from the ASCEND (NCT02970318), ALPINE (NCT03734016), RESONATE (NCT01578707), and MURANO (NCT02005471) trials, acalabrutinib, zanubrutinib, ibrutinib, and venetoclax with or without rituximab are preferred options in this treatment setting. Compared to ibrutinib, second-generation BTKis offer more favorable AE profiles with the potential for improved efficacy in some patients.<sup>25</sup> In patients with R/R CLL, use of zanubrutinib has demonstrated higher ORR and longer PFS than has ibrutinib therapy, including in patients with del(17p) or *TP53* mutations.<sup>34</sup> Updated trial results appear in **TABLE 3**.<sup>34-40</sup>

### NONCOVALENT BTK INHIBITORS IN CLL

The development of treatment resistance or intolerance can lead to treatment failure in patients receiving BTKi therapy. Prolonged treatment with ibrutinib can lead to the development of acquired mutations, such as the C481 mutation in the *BTK* gene, a common cause of BTKi-associated treatment resistance in CLL.<sup>41,42</sup> Pirtobrutinib is a noncovalent, reversible BTKi that does not require C481 binding to elicit inhibitory activity, thereby allowing for equipotent inhibitory effects in both wild-type and *BTK* C481-mutated disease.<sup>20,43</sup>

The BRUIN 1/2 trial also investigated the safety and efficacy of pirtobrutinib in 170 patients with R/R CLL who received at least 2 prior lines of therapy (median, 3 lines; range, 1-11 lines), including a prior BTKi (86%), an anti-CD20 mAb (90%), or chemotherapy (82%).<sup>44</sup> Updated results presented at the 2022 European Hematology Association Congress demonstrated an ORR of 63% among the 139 efficacy-eligible patients and 62% among the 121 patients who had received BTKi treatment. Overall, pirtobrutinib was well-tolerated, with neutropenia (10%) being the most common TEAE of grade 3 or greater; treatment-related

hemorrhage and hypertension were reported in 2% and 1% of patients, respectively.<sup>44</sup>

BRUIN CLL-321 (NCT04965493) is an ongoing, randomized, phase 3 trial evaluating the addition of pirtobrutinib to fixed duration venetoclax plus rituximab in patients with previously treated CLL.<sup>43</sup> Target enrollment is approximately 600 patients; randomization will be stratified according to del(17p) and prior BTKi status. Patients excluded from the study include those with CNS disease, Richter transformation, receipt of ASCT or CAR T-cell therapy within 60 days of therapy initiation, or prior BCL2 inhibitor or noncovalent BTKi treatment. The primary study end point is PFS; key secondary end points include ORR, OS, safety, and patient-reported outcomes.<sup>43</sup>

### STAKEHOLDER INSIGHTS

Some faculty indicated that acalabrutinib is the preferred BTKi for R/R CLL. Most patients remain on BTKi treatment for an extended period of time, and **Ramakrishnan** emphasized the importance of tolerability in BTKi selection. In his experience, the lowest discontinuation rates are with acalabrutinib. However, **Allan** indicated that he has seen better tolerability with zanubrutinib than with acalabrutinib and that zanubrutinib allows for easier dose reductions. In light of BTK occupancy and ALPINE trial data, experts noted that zanubrutinib may be preferred for patients with more aggressive disease (eg, with del[17p]).

Regarding the role of venetoclax in R/R CLL, **Modi** noted he opts for continuous therapy until progression occurs in patients who are MRD-positive. Other faculty have used venetoclax as monotherapy, as an addition to zanubrutinib, or in combination



**TABLE 3.**  
SUMMARY OF UPDATED TRIAL DATA IN RELAPSED/REFRACTORY CLL<sup>34-40</sup>

Trial name (NCT number)	Intervention	Population	Efficacy	Safety <sup>a</sup>
RESONATE (NCT01578707)	IBR vs OFA	R/R CLL (N = 391)	<i>IBR vs OFA</i> ORR: 91.0% vs NR mPFS: 44.1 mo vs 8.1 mo mOS: 67.7 mo vs 65.1 mo  With del(17p)/TP53 mutation: mPFS, 40.6 mo vs NR	TEAEs of interest (AG/G ≥ 3): INF: NR/45.0% AFib: 4.0%/0% HTN: 21.0%/11.0% HEM: 10.0%
Phase 2 study (NCT03206918)	ZANU	R/R CLL (N = 91)	ORR: 87.9% PFS (36-mo est): 68.1%	TEAEs of interest: AFib: 1 patient
ASCEND (NCT02970318)	ACALA vs IdR/BR	R/R (N = 310)	<i>ACALA vs IdR/BR</i> ORR: 83.0% vs 84.0% PFS (42.0-mo est): 62.0% vs 19.0% OS (42.0-mo est): 78.0% vs 65.0%	TEAEs of interest (AG/G ≥ 3): INF: 68.0%/29.0% AFib: 8.0%/1.0% HTN: 8.0%/5.0% HEM: 3.0%
ELEVATE-RR (NCT02477696)	ACALA vs IBR	R/R CLL (N = 533)	<i>ACALA vs IBR</i> ORR: 81.0% vs 77.0% mPFS: 38.4 mo vs 38.4 mo mOS: NR vs NR  With del(17p)/TP53 mutation: mPFS: 32.9 mo vs 27.6 mo	TEAEs of interest (AG/G ≥ 3): INF: NR/30.8% AFib: 9.0%/4.5% HTN: 8.6%/4.1% HEM: 4.5%
ALPINE (NCT03734016)	ZANU vs IBR	R/R CLL (N = 652)	<i>ZANU vs IBR</i> ORR: 86.2% vs 75.7% PFS (24 mo): 78.4% vs 65.9% mOS: NR vs NR  With del(17p)/TP53 mutation: PFS (24 mo): 72.6% vs 54.6%	TEAEs of interest (AG/G ≥ 3): INF: 71.3%/26.5% AFib: 5.2%/2.5% HTN: 23.5%/15.1% HEM: 2.9%

ACALA, acalabrutinib; AFib, atrial fibrillation; AG, any grade; CLL, chronic lymphocytic leukemia; del(17p), deletion in the short arm of chromosome 17; est, estimate; G, grade; HEM, major hemorrhage; HTN, hypertension; IBR, ibrutinib; IdR/BR, idelalisib plus rituximab or bendamustine plus rituximab; INF, infection; mo, month(s); mOS, median overall survival; mPFS, median progression-free survival; NCT, National Clinical Trial; NR, not reported; OFA, ofatumumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TEAEs, treatment-emergent adverse events; TN, treatment naive; ZANU, zanubrutinib.

<sup>a</sup>Results reported for study treatment arm(s)

with rituximab or obinutuzumab.

**Torka** expressed a potential role for using MRD to guide the duration of treatment with venetoclax. **Portell** noted the potential for patients with MRD-negative status to relapse following discontinuation of venetoclax. Other experts shared reservations regarding MRD-guided treatment duration, especially in patients with aggressive disease or Richter transformation.

**Roeker** asked the panelists where pirtobrutinib may fit into the treatment landscape of CLL. Faculty agreed that pirtobrutinib is

well-tolerated, which highlights its role in treating patients intolerant of covalent BTKis. Pirtobrutinib activity does not rely on C481 site binding; thus, **Flinn** noted a role for pirtobrutinib in covalent BTKi-refractory CLL. **Allan** expressed a role for doublet therapy with pirtobrutinib and venetoclax in patients who progress on zanubrutinib.

### EMERGING TREATMENT STRATEGIES IN CLL

Faculty discussed several emerging therapies for CLL being investigated in ongoing trials. These agents include nemtabrutinib, NVG-111 (a bispecific

T-cell engager [BiTE]), and NX-2127.

Nemtabrutinib is a noncovalent, reversible BTKi that can elicit inhibitory activity with both wild-type and *BTK* C481 mutations. Initial results from the phase 1/2 BELLWAVE-001 trial (NCT03162536) demonstrated an ORR of 56% with a median DOR 24.4 months and a median PFS of 26.3 months with nemtabrutinib in patients with R/R CLL.<sup>45</sup> Treatment-related hypertension occurred in 10% of patients, and the most common TRAEs of grade 3 or greater were neutropenia (17%), thrombocytopenia (5%), and lymphocytosis (5%).<sup>45</sup>

Early results from a first-in-human phase 1 study (NCT04763083)

presented at ASH 2022 showed that NVG-111, an anti-ROR1-CD3 BiTE, was generally well-tolerated and had a manageable safety profile in patients with R/R CLL.<sup>46</sup> The most frequently reported AEs were grade 1 or 2 nausea (70%), headache (60%), fatigue (50%), and thrombocytopenia (30%). Other AEs of interest included CRS (grade 1/2, 40%) and immune effector cell-associated neurotoxicity syndrome-like symptoms (grade 3, 1 patient).<sup>46</sup>

## LOOKING AHEAD

In MCL and CLL, the development of noncovalent BTKis along with novel emerging therapies offer new therapeutic strategies.

In MCL, there remains a need for improved treatment options for patients with high-risk features such as *TP53* mutations and for those in the postcovalent BTKi setting who are candidates for CAR T-cell therapy.

In CLL, more in-depth conversations are needed regarding choice of BTKi therapy and appropriate treatment options in patients who progress on or are intolerant of BTKis. Effective treatment strategies for patients with double-refractory CLL remains a key unmet need. ■

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