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Consensus Recommendations from the 2024 Lymphoma Research Foundation Workshop on Treatment Selection and Sequencing in CLL or SLL

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Abstract:
Over the past decade, treatment recommendations for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) have shifted from traditional chemoimmunotherapy to targeted therapies. Multiple new therapies are commercially available, and in many cases a lack of randomized clinical trial data makes selection of the optimal treatment for each patient challenging. Additionally, many patients continue to receive chemoimmunotherapy in the US, suggesting a gap between guidelines and real-world practice. The Lymphoma Research Foundation convened a workshop comprised of a panel of CLL/SLL experts in the US to develop consensus recommendations for selection and sequencing of therapies for patients with CLL/SLL in the US. Herein, the recommendations are compiled for use as a practical clinical guide for treating providers caring for patients with CLL/SLL, which complement existing guidelines by providing a nuanced discussion relating how our panel of CLL/SLL experts in the US care for patients in a real-world environment.

Conflict of interest: COI declared - see note

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Consensus Recommendations from the 2024 Lymphoma Research Foundation Workshop on Treatment Selection and Sequencing in CLL or SLL

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ABSTRACT

Over the past decade, treatment recommendations for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) have shifted from traditional chemoimmunotherapy to targeted therapies. Multiple new therapies are commercially available, and in many cases a lack of randomized clinical trial data makes selection of the optimal treatment for each patient challenging. Additionally, many patients continue to receive chemoimmunotherapy in the US, suggesting a gap between guidelines and real-world practice. The Lymphoma Research Foundation convened a workshop comprised of a panel of CLL/SLL experts in the US to develop consensus recommendations for selection and sequencing of therapies for patients with CLL/SLL in the US. Herein, the recommendations are compiled for use as a practical clinical guide for treating providers caring for patients with CLL/SLL, which complement existing guidelines by providing a nuanced discussion relating how our panel of CLL/SLL experts in the US care for patients in a real-world environment.

INTRODUCTION

Therapeutic advances in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) have led to a paradigm shift from chemoimmunotherapy to targeted therapies and improved patient outcomes. However, treatment selection is increasingly complex, and many patients in the United States (US) continue to receive chemoimmunotherapy, suggesting a gap between guidelines and real-world practice.[1,2] Therefore, the Lymphoma Research Foundation (LRF) convened a working group to develop practical recommendations for treatment selection and therapeutic sequencing for patients with CLL/SLL, focusing on US providers and patients.

METHODOLOGY

An adapted Delphi method was utilized to develop consensus. The working group reviewed the objectives, providing initial feedback to J.D.S. and D.M.S. who developed the program. Workshops were moderated by J.D.S./D.M.S (1/10/2024, 1/29/2024, 3/25/2024). The working group members were selected to ensure broad representation by geography and institutions, and LRF Scholar Award Recipients with a career interest in CLL/SLL were included. Relevant literature was reviewed, and the panel completed *ad hoc* anonymous questionnaires before/after each conference, which served as the basis for consensus. Areas of disagreement/alignment were discussed until consensus was reached (unanimous agreement attempted; ≤1 dissent permitted). J.D.S./D.M.S. wrote the manuscript, which panel members edited to ensure it reflected consensus. Equivalent options were listed alphabetically. Non-binding/non-iterative feedback was solicited from industry (Supplement S9). Although for some therapies high copays can be prohibitive, co-pay assistance programs are available through foundations and free drug programs are available through pharmaceutical companies, thus the panel provided a reference to the **LRF Patient Assistance Program** but did not consider cost/access in consensus development. **English and Spanish patient materials** incorporated feedback from individuals without medical training. LRF and Co-Chairs (J.D.S./D.M.S.) will meet annually and on an *ad hoc* basis following major advances in CLL/SLL to determine whether to convene a LRF Workshop to update consensus recommendations.

CONSENSUS RECOMMENDATIONS

Section 1. Decision to initiate therapy.

Our approach adheres to International Workshop on CLL (iwCLL) guidelines 2018 for initiation of therapy for CLL/SLL.

iwCLL criteria for therapy initiation are summarized in Table S1.[3] Several randomized trials have evaluated early treatment in asymptomatic patients with CLL/SLL, uniformly demonstrating that early treatment increases toxicity without improving overall survival (OS; Table S2).[4-7] While most evaluated early traditional chemotherapy, this also includes the CLL12 trial comparing ibrutinib vs placebo, which demonstrated no OS difference.[7,8] We await results from the S1925 trial, which is evaluating early fixed-duration venetoclax-obinutuzumab (Ven-O) in asymptomatic patients with high/very high-risk CLL/SLL using the CLL-International Prognostic Index (CLL-IPI) compared to initiation of Ven-O at the time of meeting traditional iwCLL criteria, in which the primary endpoint is OS (Table 1).[9]

Section 2. Recommended frontline therapeutic options.

This section describes the frontline therapies we recommend for patients with CLL/SLL.

2.1. When initial treatment of CLL/SLL is advised, we advise against the use of traditional chemotherapy agents such as fludarabine, cyclophosphamide, bendamustine, and chlorambucil.

We advise against traditional chemoimmunotherapy in CLL/SLL because randomized phase 3 trials have consistently demonstrated that use of targeted therapy 1) prolongs progression-free survival (PFS), and in some cases OS, and 2) demonstrates a favorable safety profile compared with chemoimmunotherapy (Table S4).[10-26]

Historically, we considered FCR (fludarabine, cyclophosphamide, rituximab) for young, fit patients with low-risk CLL/SLL (IGHV mutated; absence of del(17p)/del(11q)), where there is potential for functional cure (54% progression-free without recurrences >12 years).[27] However, we do not recommend FCR given the availability of alternative effective treatment options, as well as prolonged immunosuppression and secondary cancers associated with FCR, with secondary myelodysplasia/acute myeloid leukemia occurring in ~5% of patients.

2.2. When initial treatment of CLL/SLL is advised, we recommend targeted agents such as Ven-O, acalabrutinib ± obinutuzumab, or zanubrutinib.

Prospective data directly comparing Ven-O, acalabrutinib ± obinutuzumab, and zanubrutinib for the frontline treatment of CLL/SLL are unavailable to determine a single standard initial treatment in CLL/SLL. Section 4 describes how to develop an individualized treatment plan. Table S3 summarizes dose/administration recommendations.

Differences in treatment duration limit direct comparisons of these regimens, with cBTKi administered continuously until progression/intolerance, and Ven-O administered over 12 months.[20-26,28-30] We await results from the CLL17 trial which randomizes patients with CLL/SLL requiring frontline therapy to receive ibrutinib (continuous), Ven-O (12 months), or venetoclax-ibrutinib (15 months), which may start to address this knowledge gap.[31]

Fixed-duration therapy with ibrutinib and venetoclax (IV) is available in Europe and the United Kingdom based on the GLOW trial.[32] IV has not been approved in the US, and was not included as a preferred frontline therapy by our panel. Results from the AMPLIFY phase 3 trial of acalabrutinib and venetoclax (AV) ± obinutuzumab vs chemoimmunotherapy in treatment-naïve CLL/SLL are expected soon. As a result, AV might emerge as an attractive option for patients who favor time-limited therapy and prefer oral therapy alone, and whose past medical history, active comorbidities, and concomitant medications make them good candidates for cBTKi-based therapy (see Section 4).

Section 3. Choice of cBTKi in CLL/SLL

When a covalent Bruton's tyrosine kinase inhibitor (cBTKi) is used in CLL/SLL, we recommend use of a second-generation cBTKi (acalabrutinib or zanubrutinib) over ibrutinib. We refrain from singling out acalabrutinib or zanubrutinib as the preferred second-generation cBTKi. This choice can be individualized based on review of patient co-morbidities and the safety profiles of acalabrutinib and zanubrutinib.

We recommend use of a second-generation cBTKi (acalabrutinib or zanubrutinib) over ibrutinib based on the ELEVATE-RR and ALPINE trials in patients with relapsed or refractory (RR) CLL/SLL.[33,34] Acalabrutinib and zanubrutinib were at least as effective, and better tolerated, compared with ibrutinib (Table S5). These data have been extrapolated to the frontline setting where direct head-to-head comparisons are unavailable. Ibrutinib dose optimization studies to improve safety are ongoing (NCT05963074). Without randomized data demonstrating comparable safety and efficacy, these data would not impact our recommendation to use a second-generation cBTKi.

Acalabrutinib versus ibrutinib. In ELEVATE-RR, 533 patients with RR CLL with del(17p) or del (11q) were randomized to receive acalabrutinib at 100mg by mouth (PO) twice daily (BID) or ibrutinib at 420mg PO daily (QD) continuously until progression/intolerance.[33,35] ELEVATE-RR met its primary endpoint demonstrating that the PFS for acalabrutinib was non-inferior to ibrutinib, with both arms achieving a median PFS of 38.4 months. Rates of atrial fibrillation/flutter and hypertension were lower with acalabrutinib, while rate of headache was higher.

Zanubrutinib versus ibrutinib. In ALPINE, 652 patients with RR CLL (all risk) were randomized to receive zanubrutinib at 160mg PO BID versus ibrutinib at 420mg PO QD until progression/intolerance.[34] ALPINE was designed to determine superiority of zanubrutinib for overall response rate (ORR; primary endpoint). PFS was a secondary endpoint. ALPINE met its primary endpoint with zanubrutinib resulting in higher ORR (85% versus 74%) and improved PFS (3-year PFS 65% versus 55%). Rates of atrial fibrillation/flutter were lower with zanubrutinib, while rates of hypertension were similar.

Acalabrutinib or zanubrutinib. In the absence of randomized data directly comparing acalabrutinib and zanubrutinib, despite differences in PFS outcomes between the ALPINE and ELEVATE-RR trials, our panel cannot single out either as the preferred agent. Differences between the ALPINE and ELEVATE-RR patient populations limit cross-trial comparisons. cBTKi selection is tailored to the individual patient and is often based on comorbidities and possible differences in safety profiles. For instance, acalabrutinib may be preferred in a patient with uncontrolled hypertension while zanubrutinib may be preferred in a patient with chronic/severe headaches.

Dosing of cBTKi. Acalabrutinib is administered at 100mg PO BID.[29] The majority of data supporting zanubrutinib in CLL/SLL used a dose of 160mg PO BID, informed by phase 1 data demonstrating near-complete (>95%) nodal BTK occupancy in 89% at 160mg BID vs 50% at 320mg QD (P=0.03).[36] While the zanubrutinib label was also approved with alternate dose of 320mg PO QD, a consideration for patients with poor adherence or strong preference for QD dosing, the panel recommends administering zanubrutinib at 160mg BID as in its CLL/SLL registration trials.

When to add obinutuzumab to acalabrutinib in treatment-naïve CLL/SLL. While the addition of obinutuzumab to acalabrutinib for frontline treatment of CLL/SLL may be associated with a longer PFS compared with acalabrutinib alone, the majority of the panel does not routinely add obinutuzumab. In previously untreated patients with CLL/SLL, the addition of obinutuzumab to acalabrutinib was associated with longer PFS (6-year PFS of 78% vs 62%) making this a reasonable option.[37] Despite this PFS benefit, among patients who select a cBTKi over Ven-O, many do so to avoid intravenous infusion therapy. Addition of acalabrutinib is also associated with increased toxicity. Therefore, the panel

reported that they add obinutuzumab to acalabrutinib in a minority of patients, and the most common reason provided was the presence of uncontrolled autoimmune cytopenias. While most of the evidence for an anti-CD20 mAb in refractory autoimmune cytopenias was with rituximab, small case series have demonstrated that obinutuzumab can be effective in this setting, which is consistent with our clinical experience.[38,39]

Section 4. Selection of initial therapy.

This section describes how to choose between a cBTKi or Ven-O for frontline treatment of CLL/SLL. See Section 3 for recommendations regarding when to add obinutuzumab to acalabrutinib.

4.1. Our specific treatment recommendations should be tailored to each individual patient.

Routine pretreatment assessments and their roles in estimating prognosis and selecting therapy are shown in Table 1. We individualize recommendations for each patient after considering relevant pretreatment factors (Figure 1).

4.2. Patient preference is a very important factor when selecting between a second-generation cBTKi and Ven-O as initial therapy. Key differences affecting patient preference include: 1) therapy until progression or intolerance vs time-limited therapy, 2) oral therapy alone vs addition of intravenous obinutuzumab, and 3) limited vs frequent visits/laboratories over the first eight weeks on therapy.

Most patients with CLL/SLL do not have a definitive indication for a specific frontline therapy (Figure 1B), making either a second-generation cBTKi or Ven-O reasonable options. In such cases, selection of initial therapy should be driven by patient preference, informed by understanding the treatments themselves (Figure 1A) and other patient and disease-related factors (Figure 1C).

Patients who prioritize all-oral medication without intravenous therapy or wish to avoid frequent visits and laboratory testing required over the first 8 weeks of Ven-O may prefer a second-generation cBTKi. Others place greater value on fixed-duration therapy to maximize time off therapy and may prefer Ven-O. We developed an Educational Tool, which can be shared with patients and their advocates to assist with treatment discussions.

Despite evidence that most patients with CLL/SLL want to participate in discussions regarding treatment selection, many report not having this opportunity.[40] While other factors may supersede preference and drive treatment selection for some, we strongly encourage engaging patients in treatment selection (shared decision-making).

4.3. For patients with concomitant warfarin or dual antiplatelet therapy (DAPT), a history of major bleeding with ongoing bleeding risk, or a history of ventricular arrhythmias with ongoing ventricular arrhythmia risk, we strongly recommend Ven-O over a cBTKi. While concomitant use of a non-warfarin anticoagulant or single anti-platelet therapy, or a history of atrial fibrillation or flutter (AF), influences treatment selection towards Ven-O, a second-generation cBTKi (acalabrutinib or zanubrutinib) remains a reasonable option (Table 2; Figure 1).

We recommend assessment of past medical history, active comorbidities, and concomitant medications that may influence treatment selection between a second-generation cBTKi vs Ven-O for previously untreated CLL/SLL (Table 2; Figure 1).

4.4. When considering molecular risk factors, the most impactful for treatment selection is del(17p) or TP53 mutation (TP53M)* which *influences treatment selection towards a second-generation cBTKi (acalabrutinib or zanubrutinib). Given the lack of direct comparison of a cBTKi and Ven-O in this population, and taking other factors including patient preference into account, Ven-O remains a reasonable option for patients with CLL/SLL with del(17p)/TP53M (Fig 1C).

We strongly recommend assessment of cytogenetic and molecular risk factors, including molecular analysis to assess *IGHV* mutation status, sequencing to assess *TP53* mutation status, FISH to assess 17p deletion, 11q deletion, 13q deletion, and trisomy 12, and CpG-stimulated metaphase karyotype or SNP array to assess for karyotypic complexity, which are crucial for understanding each patient's prognosis (Table 1).[41-50]

That del(17p)/*TP53M* influences treatment selection towards a second-generation cBTKi is based on prospective trials of cBTKi in del(17p) CLL/SLL, as well as subgroup analyses of other cBTKi trials, which demonstrate durable PFS (2-year PFS of ~85-90%; Table S6).[18,37,51-54] Durability of response to time-limited therapy with Ven-O in this population is less well-established. In CLL14, only 25 patients with a del(17p) or *TP53M* received Ven-O.[25] Nevertheless, the median PFS in this subgroup was 52 months, which is encouraging but less than seen with cBTKi, albeit with potential to extend benefit with retreatment. Therefore, Ven-O remains a reasonable option for patients with CLL/SLL and del(17p)/*TP53M.*

We acknowledge that direct comparisons of a cBTKi and Ven-O are not available in any molecular risk group (e.g., del(17p)/*TP53M*, unmutated *IGHV*, or increased karyotypic complexity), and these cross-trial comparisons come from small subgroup analyses in most cases. Additionally, it is particularly challenging to interpret PFS between continuous administration of a cBTKi and time-limited therapy with Ven-O where there is the potential for retreatment at progression to extend benefit. For these reasons, when the impact of a molecular risk factor on prognosis is different between a second-generation cBTKi and Ven-O, this does not establish a predictive role for guiding selection of therapy. The ongoing CLL17 study will compare the impact of Ven-O vs ibrutinib in the frontline setting but is not restricted to patients with del(17p)/*TP53M*.

Section 5. Second-line therapy after a frontline cBTKi.

This section describes panel recommendations for selecting second-line therapy following initial cBTKi. Figure 2A graphically summarizes recommendations.

5.1. For patients who require second-line treatment after frontline cBTKi, when use of an alternative cBTKi is not appropriate or preferred, we recommend venetoclax with an anti-CD20 mAb. While rituximab with venetoclax is approved for patients with relapsed or refractory CLL/SLL, the majority of the panel recommends obinutuzumab with venetoclax in this setting.

Venetoclax-rituximab (Ven-R) is approved for RR CLL/SLL based on the MURANO trial which demonstrated superior PFS compared with bendamustine-rituximab (BR; 54.7 vs 17.9 months, p<0.0001).[61,62] In MURANO, venetoclax is stopped after 2 years, with rituximab administered concurrently during the first 6 months. Importantly, MURANO included very few patients with prior cBTKi, and >95% were previously treated with chemoimmunotherapy. Single-arm prospective trials and real-world datasets have confirmed that venetoclax ± an anti-CD20 mAb is effective after a cBTKi.[63-67]

The majority of the panel recommends Ven-O for RR CLL/SLL with an obinutuzumab lead-in before the venetoclax ramp-up (CLL14 schedule) and 2 years of venetoclax (off-label; Table S3). This is based on extrapolations from the frontline setting, where obinutuzumab is more effective than rituximab (Table S8).[23,26,68] In CLL13, Ven-O was associated with higher rates of uMRD4 compared with FCR or BR in fit patients with CLL/SLL without del(17p)/*TP53M*, but Ven-R was not.[26] In CLL11, where patients with CLL/SLL and coexisting conditions were randomized to receive chlorambucil alone, or chlorambucil with either obinutuzumab or rituximab, obinutuzumab was associated with prolonged OS compared to chlorambucil alone or chlorambucil with rituximab.[68]

When patients have disease progression on a cBTKi, abrupt discontinuation may precipitate rapid progression.[69] Therefore, for patients with progression on a cBTKi, when venetoclax ± an anti-CD20 mAb is started, we continue the cBTKi until there is evidence of clinical/laboratory evidence of response (may range from 1 week to 2 months; Table 3B).

5.2. For patients who discontinue a cBTKi due to intolerance and require further CLL/SLL treatment, an alternative second-generation cBTKi (acalabrutinib or zanubrutinib) can be considered unless the reason for intolerance was a life- or organ-threatening condition.

Acalabrutinib and zanubrutinib have been evaluated in patients who are intolerant to a previous cBTKi, including in two prospective phase 2 trials (Table S7).[70-72] In the acalabrutinib study, 30% of patients experienced recurrence of the intolerance event leading to ibrutinib discontinuation. In the zanubrutinib study, 40% experienced recurrence of the intolerance event leading to ibrutinib/acalabrutinib discontinuation. Recurrence of the same intolerance event led to discontinuation in just 1 patient (grade 2 diarrhea). When the same intolerance event recurred, most were with lower severity (67-79%) and only one recurred with worse severity (increased liver function test; grade 2 on ibrutinib then grade 3 on acalabrutinib). Importantly, because 21-30% of intolerance events recurred with unchanged severity after switching to acalabrutinib or zanubrutinib, we do not advise an alternative second-generation cBTKi following life- or organ-threatening intolerance.

Section 6. Second-line therapy after frontline Ven-O

This section describes panel recommendations for selecting second-line therapy following initial Ven-O. Figure 2B graphically summarizes recommendations.

6.1. For patients who require second-line treatment after frontline Ven-O, when retreatment with venetoclax ± an anti-CD20 mAb is not preferred, we recommend a second-generation cBTKi (acalabrutinib or zanubrutinib).

Our panel recommends a second-generation cBTKi in the second-line setting after frontline Ven-O. Given the earlier introduction of cBTKi in frontline treatment of CLL/SLL, very few patients in the RR cBTKi trials had prior venetoclax. Among patients enrolled in the ELEVATE-RR and ALPINE trials (Section 3), <3% patients received prior venetoclax.[33,34] Limited data exist to estimate cBTKi efficacy after frontline Ven-O, drawn mostly from small retrospective series. In one, among 44 patients who were BTKi-naïve and previously received venetoclax in the frontline (4%) or RR (96%) setting, cBTKi had an ORR of 84% and median PFS of 32 months.[55] In another series of 23 patients who previously received venetoclax, cBTKi therapy had an ORR of 91% and median PFS of 34 months.[56] These data support the use of BTKi after venetoclax-based therapy, and the panel recommends use of a second-generation cBTKi (acalabrutinib or zanubrutinib) over ibrutinib (Section 3).

6.2. For patients previously treated with venetoclax and an anti-CD20 mAb and later have disease progression and require therapy, retreatment with venetoclax ± anti-CD20 mAb can be considered in patients who tolerated venetoclax well and whose disease did not progress within 1 year of stopping venetoclax.

Because venetoclax with obinutuzumab or rituximab are time-limited regimens, most patients with CLL/SLL discontinue venetoclax due to completion of planned therapy and are not resistant to venetoclax. In patients with subsequent disease progression who require therapy, if venetoclax was previously well-tolerated, retreatment with venetoclax ± an anti-CD20 mAb can be considered. Whether to add an anti-CD20 mAb, and the optimal treatment length, should be individualized to each patient, as described in Table 3C.

Venetoclax retreatment is supported by small datasets demonstrating frequent responses in patients requiring subsequent therapy.[57-59] The largest is a retrospective multicenter analysis of 46 patients previously treated with venetoclax-based therapy, who later had disease progression and received a second course of venetoclax.[58] Venetoclax retreatment was associated with an ORR of 80% and median PFS of 25 months. Notably, only 9% (4/46) received venetoclax retreatment after frontline venetoclax-based therapy, and the most common retreatment approach was venetoclax monotherapy (45.7%), thus these data might underestimate its efficacy. We await long-term follow-up and retreatment data from the frontline CLL14 and CLL13 studies and the ongoing ReVenG trial to refine this strategy, which includes cohorts who experienced 1-2 years and ≥2 years treatment-free interval to identify the optimal duration of remission following treatment cessation when considering venetoclax retreatment.[60]

Although there are no clear data guiding patient selection for venetoclax retreatment, previous venetoclax tolerability and the length of time from completing prior venetoclax are likely important. We reserve venetoclax retreatment for patients with ≥1 year duration of response off-treatment after prior venetoclax. This recommendation is based on measurable residual disease (MRD) analyses in patients receiving frontline Ven-O, which suggested that 1) progression occurred earlier in patients with end-of-treatment detectable MRD ($\geq 10^{-4}$; MRD4), and 2) among patients with detectable MRD4, 50% already had a rising CLL cell count.[25] These data suggest an association between early progression and subclinical resistance to venetoclax, and that patients with longer treatment-free remissions, i.e., ≥1-2

year duration of response after discontinuing venetoclax, are more likely to benefit from venetoclax retreatment.

Section 7. Second-line therapy after other therapies

7.1. Prior cytotoxic chemotherapy

Although we advise against traditional chemoimmunotherapy in CLL/SLL, we continue to see patients who require treatment for relapsed CLL/SLL who have only received prior chemoimmunotherapy. When a patient with CLL/SLL has only received prior chemoimmunotherapy and requires subsequent therapy, we recommend use of second-generation cBTKi (acalabrutinib or zanubrutinib) or venetoclax with an anti-CD20 mAb as described in Sections 6.1 and 5.1, respectively. Section 4 describes how to choose between a cBTKi or Ven-O for treatment-naïve patients with CLL/SLL and can be extrapolated here.

7.2. Prior therapy with a cBTKi and BCL2i with or without obinutuzumab

IV is approved in Europe and the UK based on the GLOW trial[32] and others have received initial therapy with a cBTKi and BCL2i with or without obinutuzumab through participation in clinical trials. The optimal second-line therapy approach for these patients is undefined. However, in the CAPTIVATE phase II trial of fixed-duration IV in patients with treatment-naïve CLL, ibrutinib retreatment had an ORR of 86% (19/22) and remissions appeared durable.[73] Given these limited data, if the cBTKi-BCL2i regimen was stopped in an ongoing response, second-line therapy options include either a second-generation cBTKi, or treatment with venetoclax ± an anti-CD20 mAb (as described in Section 6.2). Alternatively, in patients who are primary refractory to a cBTKi-BCL2i combination, additional workup may be necessary to exclude Richter transformation (Table 1) before considering subsequent treatment of CLL/SLL (see Section 8).

Section 8. Treatment sequencing after ≥2 therapies including venetoclax and a cBTKi

This section describes panel recommendations for therapy selection in patients with ≥2 prior therapies including venetoclax and a cBTKi. Transitioning to an alternate second-generation cBTKi (Section 6.2) or retreatment with venetoclax ± an anti-CD20 mAb (Section 5.2) may also be reconsidered. Figure 2 graphically summarizes panel recommendations.

8.1. For patients with CLL/SLL and two or more prior therapies including a cBTKi and venetoclax, when retreatment with venetoclax ± an anti-CD20 mAb or transitioning to an alternate cBTKi is not preferred, we recommend pirtobrutinib in most cases. In patients who are deemed good candidates, lisocabtagene maraleucel (liso-cel) should also be considered for this line or subsequent lines of therapy.

Pirtobrutinib. The noncovalent BTKi pirtobrutinib is FDA approved for patients with CLL/SLL and ≥2 prior therapies including a cBTKi and venetoclax based on the BRUIN study.[74,75] In this study, patients with prior cBTKi and venetoclax treatment (n=128) who received the recommended dose of pirtobrutinib at 200mg PO daily until progression or intolerance had an ORR of 80% (CRR=0%) with a median PFS of 16 months, without a plateau in the PFS curve.[74,76] Notably, pirtobrutinib was very well-tolerated with reported rates of any grade diarrhea, fatigue, cough, and contusion as 37%, 28%, 27%, and 26%, respectively. Grade ≥3 adverse events were limited with the most common being neutropenia in 28%, and it should be noted that many patients were neutropenic at baseline and there were very limited cases of febrile neutropenia. Non-hematologic grade ≥3 adverse events were rare, including typical BTKi AEs such as hypertension (4%) and atrial fibrillation (2%). Given that CLL is most commonly diagnosed during the seventh decade and many patients have additional medical comorbidities, the limited toxicity and ease of administration are key considerations in recommending pirtobrutinib therapy in most cases where patients need additional treatment after cBTKi and venetoclax.

Liso-cel. The anti-CD19 chimeric antigen receptor T-cell (CART) therapy liso-cel is FDA approved for patients with CLL/SLL and ≥2 prior therapies including a cBTKi and venetoclax based on the TRANSCEND-CLL 004 study.[77,78] In this study, patients with prior cBTKi and venetoclax treatment (n=50) who received liso-cel had an ORR of 44% (CRR=20%) and the median PFS was 11.9 months. In patients who achieved complete remission (CR; 20%), the median PFS was not reached with no relapses detected after 2 years of follow-up, albeit with very small sample size. In patients who achieved partial remission (PR; 24%), the median PFS was 26 months. There are limited data available to help predict which patients are most likely to achieve CR/PR. In an exploratory analysis from the TRANSCEND-CLL 004 trial, del(17p) or *TP53M*, unmutated *IGHV*, and increased karyotypic complexity were not associated with the likelihood of achieving response to liso-cel. Rather, response to liso-cel was associated with pretreatment variables indicating lower pretreatment disease burden (i.e., lower tumor measurements, β2-microglobulin [β2M], and BALL score [includes β2M and LDH]).[79]

Logistically, patients are instructed to stay in close proximity of the CART treatment center for 30 days, and many require inpatient hospitalization. Cytokine release syndrome (CRS) and neurological events (NE) occurred in 85% (8% grade ≥3) and 45% (19% grade ≥3) of patients, respectively. While CRS/NE events typically occur within the first 1-4 weeks, long-term toxicities including prolonged cytopenias (54%), grade ≥3 infections (18%), and hypogammaglobulinemia (15%) were frequent, albeit in a population enriched for prior traditional chemoimmunotherapy (89%). Liso-cel is a relatively higher-risk, higher-reward option, with long-term remissions observed in 20% of patients. This must be balanced against significant associated toxicities, which are typically seen during the first few weeks following liso-cel infusion. Although liso-cel can be administered to older patients, ideal candidates are younger and medically fit enough to tolerate the upfront toxicity of the regimen, and for those who prefer aggressive and potentially definitive, time-limited therapy.

Pirtobrutinib versus liso-cel. Pirtobrutinib and liso-cel are FDA approved in the same population (CLL/SLL with 2 prior therapies including a cBTKi and venetoclax). Randomized data is needed to determine if pirtobrutinib or liso-cel is preferred. We recommend pirtobrutinib in most cases, given its ease of administration and favorable toxicity profile, and because we currently cannot predict patients with CLL/SLL who will achieve durable remissions with liso-cel. However, some patients will prioritize a potentially definitive, time-limited therapy, especially those who are younger and medically fit, and these patients may prefer liso-cel. Finally, we recognize that pirtobrutinib has a median PFS of only 16 months, making the selection of pirtobrutinib or liso-cel one of treatment sequencing for most patients.

Bridging therapy prior to liso-cel. Although liso-cel is administered to patients with active disease including those with high disease burden, bridging therapy is often necessary as a palliative measure during liso-cel manufacturing. In pirtobrutinib-naïve patients, pirtobrutinib is an excellent option for bridging therapy which may reduce disease burden before liso-cel administration, so may be started in parallel with referral for liso-cel. In pirtobrutinib-exposed patients, other bridging therapies can be considered in consultation with a CLL expert and liso-cel provider.

8.2. For patients with CLL/SLL that is refractory to three prior therapies including venetoclax, a cBTKi, and pirtobrutinib, when treatment with liso-cel or participation in a clinical trial is not feasible or preferred, a PI3Kδ inhibitor should be considered.

The PI3Kδ inhibitors duvelisib and idelalisib ± rituximab were FDA approved based on randomized trials showing prolonged PFS compared to an anti-CD20 mAb.[80-82] PI3Kδ inhibitors have an unfavorable toxicity profile, including severe immune-mediated toxicities including colitis, hepatitis, and pneumonitis, and severe infections. The approved PI3Kδ inhibitors also have limited efficacy in CLL/SLL. The pivotal trials were completed before wide availability of cBTKi and venetoclax. In a subsequent retrospective series, the median PFS with PI3Kδ inhibitor therapy was only 5 months among patients with prior cBTKi and venetoclax (n=17).[55] In rare instances that a PI3Kδ inhibitor is administered, we utilize the PI3Kδ inhibitor white paper on managing toxicity.[83] We recommend engaging a provider experienced in monitoring for and managing PI3Kδ inhibitor toxicities.

8.3. Referral to a CLL expert to discuss whether to pursue allogeneic stem cell transplant (alloSCT) may be considered for patients with CLL/SLL who are refractory to at least 2 prior therapies including venetoclax and a cBTKi and who obtained a remission to a subsequent therapy.

AlloSCT is potentially curative in CLL/SLL, but fewer patients undergo alloSCT in the modern era.[84] A retrospective series of 65 patients with CLL/SLL who underwent alloSCT after a targeted kinase inhibitor reported a 2-year PFS and OS of 63% and 81%, and high-risk molecular features did not impact PFS.[85] Toxicity should be taken into consideration given rates of non-relapse mortality, acute graft versus host disease (GVHD) and chronic GVHD of 13%, 24%, and 27%, respectively.[85]

In one retrospective series of alloSCT in CLL/SLL, >20% bone marrow involvement pretransplant was associated with failure to engraft, which suggests that some clearance of CLL/SLL from the bone marrow is necessary pretransplant.[86] However, iwCLL response (CR vs PR) was independent of PFS rates with alloSCT after a targeted kinase inhibitor, suggesting that achieving CR is not necessary pretransplant.[85]

Our panel is more likely to consider alloSCT for patients who are young and medically fit, have high-risk cytogenetic/molecular features, or relapsed after multiple lines of targeted therapy. With the approval of liso-cel in CLL/SLL, we expect that even fewer patients with CLL/SLL will undergo alloSCT. With a growing list of effective standard and investigational therapies, we recommend referral to a CLL expert to explore the best course of action for each individual patient.

Section 9. Clinical trials.

Clinical trials should be considered for all patients with CLL/SLL, when clinical trial participation is feasible and when the study objectives are well suited to the patient's priorities.

Section 10. MRD.

Measurement of MRD provides prognostic information in patients with CLL/SLL receiving venetoclax-based therapy or liso-cel. MRD has not been shown to be prognostic for CLL patients treated with cBTKi. Our panel's recommendations regarding use of MRD in the routine care of patients with CLL/SLL are shown in Table 4.

Section 11. Resistance mutations.

In patients treated with BTKi, detecting mutations associated with BTKi resistance may provide biological information about a patient's disease and potential emerging resistance. However, patients may continue to respond to BTKi despite mutations in *BTK* and *PLCG2*, and their presence should not currently be the sole reason to change therapy.

CONCLUSION

Treatment selection should be individualized for patients with CLL/SLL. Pretreatment assessment should include clinical evaluation and testing of cytogenetic and molecular features. Line of treatment, previous treatments, comorbidities, and concomitant medications should be considered when selecting treatment, and shared decision-making used to incorporate patient preferences. Much research remains ongoing (Table 5), and we will reconvene the LRF CLL Working Group as the treatment landscape evolves for patients with CLL/SLL.

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AUTHOR CONTRIBUTIONS

Jacob Soumerai was Chair of the LRF Workshop, developed the program and questionnaires, co-moderated the workshop discussions, served as a panel member, and co-wrote the first draft of the manuscript. Deborah Stephens was Co-Chair of the LRF Workshop, developed the program and questionnaires, co-moderated the workshop discussions, served as a panel member, and co-wrote the first draft of the manuscript. Jennifer R. Brown was Senior Advisor and LRF Scientific Advisory Board Member who contributed to developing the program, served as a panel member, and critically revised the manuscript. Jacqueline Barrientos was Lead for Spanish Language materials, served as a panel member, and critically revised the manuscript. Inhye Ahn, Catherine Coombs, Douglas Gladstone, Marc Hoffman, Adam Kittai, Ryan Jacobs, Andrew Lipsky, Krish Patel, Joanna Rhodes, Alan Skarbnik, Meghan Thompson, Daniel Ermann, Patrick Reville, and Harsh Shah served as panel members, presented relevant literature at the LRF Workshop, and critically revised the manuscript.

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FIGURE LEGENDS

Figure 1: When to use a covalent BTK inhibitor vs venetoclax plus obinutuzumab in CLL or SLL.
We individualize treatment recommendations for each patient after considering relevant pretreatment factors. **(A)** Patient preference is a very important factor when selecting between a cBTKi and Ven-O as initial therapy. Key differences affecting patient preference include: 1) therapy until progression or intolerance vs time-limited therapy, 2) oral therapy alone vs addition of intravenous obinutuzumab, and 3) limited vs frequent visits/laboratory testing over the first eight weeks on therapy **(refer to Section 4.2)**. **(B)** For patients with concomitant warfarin or dual antiplatelet therapy, or a history of major bleeding with ongoing bleeding risk, or a history of ventricular arrhythmias with ongoing ventricular arrhythmia risk, we strongly recommend Ven-O over a cBTKi. While concomitant use of a non-warfarin anticoagulation or single anti-platelet therapy, or a history of atrial fibrillation or flutter, influences treatment selection towards Ven-O, a second-generation cBTKi (acalabrutinib or zanubrutinib) remains a reasonable option **(refer to Section 4.3)**. **(C)** When considering these molecular risk factors, the most impactful for treatment selection is 17p deletion or *TP53* mutation (del(17p)/*TP53M*) which influences treatment selection towards a second-generation cBTKi (acalabrutinib or zanubrutinib). Given the lack of direct comparison of a cBTKi and Ven-O in this population, and taking other factors including patient preference into account, Ven-O remains a reasonable option for patients with CLL/SLL with del(17p)/*TP53M* **(refer to Section 4.4)**.

Figure 2: Treatment algorithms for CLL or SLL.
(1) Our approach adheres to the iwCLL guidelines 2018 for the initiation of therapy for CLL/SLL **(refer to Section 1; Table S1)**; **(2)** For patients with CLL/SLL who discontinue therapy for intolerance, a treatment holiday can be considered **(refer to Table 3A)**; **(3)** When initial treatment of CLL/SLL is advised, we recommend targeted agents such as venetoclax with obinutuzumab, acalabrutinib with or without obinutuzumab, or zanubrutinib **(refer to Section 2)**; **(4)** For patients who are previously treated with venetoclax and an anti-CD20 mAb and later progress and require therapy, retreatment with venetoclax ± anti-CD20 mAb can be considered in patients who tolerated venetoclax well and whose disease did not progress within one year of stopping venetoclax **(refer to Section 6.2)**; **(5)** For patients who require second-line treatment after frontline venetoclax and obinutuzumab, when retreatment with venetoclax ± an anti-CD20 mAb is not preferred, we recommend a second-generation cBTKi (acalabrutinib or zanubrutinib) **(refer to Section 6.1)**; **(6)** For patients who discontinue a cBTKi due to intolerance and require further CLL/SLL treatment, an alternative second-generation cBTKi (acalabrutinib or zanubrutinib) can be considered unless the reason for intolerance was a life or organ-threatening condition **(refer to Section 5.2)**; **(7)** For patients with CLL/SLL and two prior therapies including a cBTKi and venetoclax, when retreatment with venetoclax ± an anti-CD20 mAb or transitioning to an alternate cBTKi is not preferred, we recommend pirtobrutinib in most cases. In patients who are deemed good candidates, lisocabtagene maraleucel should also be considered for this line or subsequent lines of therapy **(refer to Section 8.1)**. See also Special Situations regarding use of pirtobrutinib in patients who require treatment after prior cBTKi with medical contraindication to venetoclax-based therapy **(refer to Table 3D)**; **(8)** For patients with CLL/SLL that is refractory to three prior therapies including venetoclax, a cBTKi, and pirtobrutinib, when treatment with lisocabtagene maraleucel or participation in a clinical trial is not feasible or preferred, a PI3Kδ inhibitor should be considered **(refer to Section 8.2)**; **(9)** Referral to a CLL expert to discuss whether to pursue allogeneic stem cell transplant may be considered for patients with CLL/SLL who are refractory to at least 2 prior therapies including venetoclax and a cBTKi and obtained a remission to a subsequent therapy **(refer to Section 8.3)**. **(10)** Clinical trials should be considered for all patients with CLL/SLL, when clinical trial participation is feasible and when the study objectives are well suited to the patient's priorities **(refer to Section 9)**; **(11)** While the addition of

obinutuzumab to acalabrutinib for frontline treatment of CLL/SLL may be associated with a longer PFS compared with acalabrutinib alone, the majority of the panel does not routinely add obinutuzumab due to potential added toxicity and the requirement for patients to receive intravenous infusion therapy; currently, the most common reason our panel adds obinutuzumab to acalabrutinib is the presence of uncontrolled autoimmune cytopenias **(refer to Section 3)**; **(12)** While rituximab with venetoclax is approved for patients with relapsed or refractory CLL/SLL, the majority of the panel recommends obinutuzumab with venetoclax in this setting **(refer to Section 5.1)**. *, For patients previously treated with ibrutinib in place of acalabrutinib or zanubrutinib, follow guidance as if they received a second-generation covalent BTK inhibitor.

Table 1: Pretreatment patient and disease assessments in CLL or SLL

Assessment	Description and role in prognosis and treatment selection
Patient preference	
Shared decision-making discussion	As there are frequently multiple reasonable treatment options for patients with CLL/SLL, patients should be engaged in treatment discussions at all lines of therapy. This is especially crucial in the front-line setting, when deciding between a cBTKi and venetoclax-obinutuzumab (Section 4.2; Figure 1A) and in the third line setting for patients with prior venetoclax and a cBTKi, when deciding between pirtobrutinib and liso-cel (Section 6.1).
Performance status and physical exam	
ECOG performance status	We assess performance status prior to each line of therapy (Supplemental Table S12).
Physical exam	We evaluate for distribution and size of lymphadenopathy, splenomegaly, in addition to a complete physical examination (e.g., skin, head/neck, heart, lungs, abdomen).
Feasibility	
Transportation to medical center	**Venetoclax ± anti-CD20 mAb:** Frequent visits are required during the ramp-up.
Resources at treating facility	**Venetoclax ± anti-CD20 mAb:** Facility must have ability to obtain STAT labs and interventions if needed based on results during the ramp-up. **Liso-cel:** Facility must be accredited for CAR T cell therapy administration.
Financial implications	**High copays for oral therapies:** High copays can be prohibitive for some patients, although co-pay assistance programs are available through foundations and free drug programs are available through pharmaceutical companies to address this. Refer to **LRF patient assistance**. **Liso-cel:** Patient must have companion and remain within 2 hours of the facility for 1 month from cell infusion, which may require temporary leave from work for patient and companion.
Comorbidities	
Atrial fibrillation or flutter Heart failure Hypertension Major bleeding Ventricular arrhythmia	We evaluate for past medical history, active comorbidities, and concomitant medications that can influence treatment selection between a second-generation cBTKi vs venetoclax-obinutuzumab for previously untreated patients with CLL/SLL (Table 3; Figure 1). Additional workup ± referral to relevant consultants, e.g., cardio-oncology, may be helpful based on initial evaluation.

Concomitant medications	
Anticoagulation Warfarin LMWH, DOACs Antiplatelet therapy Dual antiplatelet therapy Single antiplatelet therapy Drug interactions	Careful review of medications is necessary prior to each therapy, as concomitant administration of warfarin, a non-warfarin anticoagulant, single or dual antiplatelet therapy, may influence treatment selection or require modification (Section 4.3; Figure 1). Additionally, we recommend screening patient medications for potential interactions with the therapies under consideration. When interactions exist, we work with prescribing providers to determine if there are acceptable alternatives, and with oncology pharmacy colleagues to determine impact on dosing.
Organ function	
Kidney and liver function	We obtain a comprehensive metabolic panel to assess for kidney and liver dysfunction and follow the treatment package inserts for dosing.[28-30,87] Kidney dysfunction can also increase TLS risk.
Disease burden	
Hematologic function	In patients with significant neutropenia, anemia, or thrombocytopenia, a bone marrow biopsy with aspirate is useful to determine the direct cause, such as CLL/SLL-related causes (e.g., marrow infiltration, splenic sequestration, autoimmune hemolytic anemia, or immune thrombocytopenia) vs other causes (e.g., myelosuppression or myelodysplasia from prior treatment, or alternative causes).
CT imaging	Baseline CT scan may be useful at diagnosis for patients with palpable lymphadenopathy or splenomegaly, or if warranted clinically based on symptoms. Pretreatment CT imaging should be obtained in patients considering treatment with venetoclax ± an anti-CD20 mAb to assess TLS risk. CT imaging is usually not required for diagnosis, serial monitoring, surveillance, routine monitoring of treatment response, or progression.
TLS risk	Greater disease burden measured by CT imaging (e.g., LN ≥10 cm or LN ≥5 cm with ALC ≥25,000/μ l as defined in the venetoclax package insert), and presence of significant kidney dysfunction, may increase TLS risk. We follow treatment package inserts for TLS monitoring and preventive measures.
Related conditions	
Autoimmune complications	Presence of clinically significant autoimmune complications can influence treatment selection toward a therapy that includes an anti-CD20 mAb (Section 3).

Molecular testing	
IGHV mutation status	**Diagnosis:** We assess IGHV mutation status at diagnosis given association with time to initial therapy. As IGHV mutation status is a fixed risk factor, this is assessed once, and not repeated with subsequent therapies.
Testing for mutations in *TP53*	**Diagnosis:** Although we often perform *TP53* mutation testing at diagnosis, we acknowledge a *TP53* mutation would not impact management for a patient who does not meet iwCLL 2018 criteria to initiate therapy. **Prior to each line of therapy:** We perform *TP53* mutation testing prior to each line of therapy, as presence of a *TP53* mutation can influence treatment selection (Section 4.4; Figure 1C). Some panels include additional genes *ATM*, *NOTCH1*, *SF3B1*, and *RAS/RAF* mutations, which provide additional biological information about a patient's disease, but these do not impact patient management. **Previously treated with a BTK inhibitor:** For patients who were previously treated with a BTK inhibitor, detecting mutations in *BTK and/or PLCG2* associated with resistance to BTK inhibitors may provide biological information about a patient's disease and potential emerging resistance, but patients may continue to respond to BTK inhibitors despite the detection of these mutations. (Section 11).
FISH for 17p del, 11q del, +12, and 13q del, and for t(11;14) if applicable	**Diagnosis:** Although we often obtain FISH to assess for 17p deletion, 11q deletion, 13q deletion, and trisomy 12, prior to each line of therapy, we acknowledge a 17p deletion would not impact management for a patient who does not meet iwCLL 2018 criteria to initiate therapy. **Prior to each line of therapy:** We obtain FISH to assess for 17p deletion, 11q deletion, 13q deletion, and trisomy 12, prior to each line of therapy, as presence of 17p deletion can influence treatment selection (Section 4.4; Figure 1C). While an 11q deletion carried a negative prognosis with traditional chemoimmunotherapy, this does not appear so with modern therapies.[88] **Note regarding t(11;14):** FISH for t(11;14) may be necessary to evaluate for mantle cell lymphoma, if CLL is otherwise diagnosed in peripheral blood only. FISH for t(11;14) is typically sufficient to rule out mantle cell lymphoma, although in some cases (e.g., when circulating disease immunophenotype is otherwise typical of mantle cell lymphoma (e.g., CD200 negative and CD23 negative) histologic confirmation may be necessary.

CpG-stimulated karyotype	**Diagnosis:** We obtain CpG-stimulated metaphase karyotype or SNP array to assess for karyotypic complexity at diagnosis. However, these results would not impact management for a patient who does not meet iwCLL 2018 criteria to initiate therapy. **Prior to each line of therapy:** We obtain CpG-stimulated metaphase karyotype or SNP array to assess for karyotypic complexity, as this is relevant to understanding prognosis. However, this does not currently impact treatment selection (Section 4.4)**.**
Prognostic systems	
CLL-IPI score	The CLL-IPI is a validated prognostic model for patients with CLL/SLL receiving front-line therapy, where it predicts progression-free survival (targeted therapies or traditional chemotherapy) ± overall survival (traditional chemotherapy), as well as for treatment-naïve patients on active surveillance, where it predicts time to initial therapy.[49,50,89] The risk score is available on **Calculate by QxMD**.
BALL risk score	The BALL score was derived in patients with RR CLL/SLL receiving cBTKi, and has been validated for patients with relapsed or refractory CLL/SLL on a cBTKi, PI3Kδ , venetoclax-based therapy, where it is prognostic for overall survival.[90,91] Additionally, a low-risk BALL score (0-1) is associated with a higher likelihood of achieving response to liso-cel.[79] The risk score is available on **Calculate by QxMD**.
4-factor model	The 4-factor model was derived and validated in patients with CLL/SLL receiving ibrutinib, where it is prognostic for progression-free survival, overall survival, and cumulative incidence of *BTK* and *PLCG2* mutations.[92]
Suspicion for Richter transformation	
Assess for clinical suspicion of Richter transformation to DLBCL or HL.	Richter transformation should be considered in patients with B-symptoms, rapid progression, asymmetric progression, or significantly elevated LDH without an alternative cause (e.g., presence of hemolysis)
FDG-PET/CT imaging to direct	FDG-PET imaging should be obtained if Richter transformation is suspected. As CLL/SLL is typically not hypermetabolic on FDG-PET imaging, we use FDG-PET/CT imaging to identify more FDG-avid sites of

biopsy	disease for biopsy to exclude Richter transformation (excisional biopsy preferred when feasible).

Table 2: Past medical history, active co-morbidities and concomitant medications, and therapy selection

Past medical history, active co-morbidities and concomitant medications, and therapy selection
Non-warfarin anticoagulant and/or single antiplatelet therapy
While bleeding risk appears lower with acalabrutinib or zanubrutinib compared with ibrutinib, major bleeding still occurs in 3-5% of patients.[29,30,93] Bleeding risk is increased with coadministration of a non-warfarin anticoagulant or antiplatelet therapy, which influences treatment selection toward Ven-O, but the absolute difference in major bleeding risk is low (<1-2%) and a second-generation cBTKi remains a reasonable option.[29,93] It is also important to clarify the indication for anticoagulation/antiplatelet therapy, and whether its continued use is needed.
Warfarin anticoagulant
Our recommendation against concomitant warfarin with cBTKi comes from early phase 1 trials of ibrutinib, which reported subdural hematomas in patients receiving warfarin, leading subsequent trials to exclude concomitant warfarin.[94] When a cBTKi is being considered in a patient on warfarin, which we consider a contraindication, use of an alternative anticoagulant is often acceptable, and even preferable for many indications.
Dual antiplatelet therapy
Data regarding safety of concurrent dual antiplatelet therapy and cBTKi is limited, as dual antiplatelet therapy use was very rare in cBTKi trials. However, major bleeding risk may already be increased up to ~2-fold with dual antiplatelet therapy vs aspirin, without addition of a cBTKi which leads to additional antiplatelet effect.[95] Therefore, we strongly recommend Ven-O over a cBTKi in patients on dual antiplatelet therapy.
Bleeding history
A history of major bleeding who have ongoing risk, e.g., due to an underlying bleeding disorder or uncontrolled bleeding source, have generally been excluded from clinical trials of cBTKi. Therefore, we strongly recommend use of Ven-O over a cBTKi in these patients.[10-22,33-35] Preexisting bruising or petechiae alone does not predict major bleeding and should not influence treatment selection.
Atrial fibrillation or flutter history
AF risk is lower with acalabrutinib or zanubrutinib compared with ibrutinib (2% vs 9% cumulative incidence at 12 months).[33-35,96] Patients with persistent or paroxysmal AF may be safely treated with a second-generation cBTKi, although this can occasionally precipitate recurrent AF, and use of anticoagulation or antiplatelet therapy for AF stroke reduction increases bleeding risk.
Ventricular arrhythmia history
Ventricular arrhythmias are very rare, 6-8 per 1000 person-years with ibrutinib, and occurring less frequently with acalabrutinib or zanubrutinib.[97-99] Risk factors for cBTKi-related ventricular arrhythmias are largely unknown, and ventricular arrhythmias can occur in patients without known cardiac disease. We strongly recommend against cBTKi use in patients with a history of ventricular arrhythmias unless the underlying cause is addressed.
Hypertension
Hypertension does not influence our treatment selection toward Ven-O or a cBTKi, in part because acalabrutinib has a lower incidence of hypertension compared with ibrutinib, making it an appealing cBTKi option for patients with uncontrolled or difficult-to-manage hypertension.[33,35]
Heart failure
Heart failure is not a single disease and can have heterogeneous clinical manifestations, each interacting differently with treatment risks. For instance, while the presence of volume overload may complicate intravenous fluid administration for venetoclax-treated patients with higher risk of tumor lysis syndrome, this short-term risk may be preferred as baseline heart failure increases cardiovascular risks associated with BTKi.

Table 3: Special treatment situations

Topic	Consensus Statement	Justification and supporting literature
(A) When to consider a treatment holiday	**For patients with CLL/SLL who discontinue therapy for intolerance, a treatment holiday can be considered.**	This recommendation is based on the observation that among patients with CLL/SLL whose disease is responding to therapy, and who discontinue therapy for intolerance, some have durable treatment-free remissions. Little data exists to guide selection of patients for a treatment holiday. Our panel considers several factors, e.g., duration of therapy and quality of response, in an effort to predict which patients will remain progression-free off therapy. In a single-arm study of elective ibrutinib discontinuation after ≥6 years of continuous therapy, most had decreased or stable disease after a ≥1 year treatment-free interval.[100] The panel is also more inclined to consider a treatment holiday in patients without high-risk molecular features, based on posttreatment MRD kinetics data from MURANO suggesting faster MRD doubling in the presence of high-risk molecular features.[59]
(B) How to transition from a cBTKi to venetoclax ± anti-CD20 mAb	**In patients with progressive disease on a cBTKi who are recommended venetoclax ± an anti-CD20 mAb, the panel recommends a period of overlapping therapy, with the cBTKi generally stopped once there is evidence of disease control, which can range from 1 week to 2 months.**	When CLL becomes resistant to a cBTKi, there are often subclones of resistant CLL cells and subclones of cells that are still responsive to the cBTKi. As such, abrupt discontinuation of a cBTKi without transition to another therapy can lead to rapid progression of CLL.[69] Safety data are available for each approved cBTKi combined with venetoclax and an anti-CD20 mAb.[101-103] We recommend initiating venetoclax ± an anti-CD20 mAb prior to stopping the cBTKi, as a period of overlap can prevent rapid progression of disease. The cBTKi can be stopped once there is evidence of disease control (e.g., reduction of lymphocyte count, lymphadenopathy, splenomegaly, and/or CLL-related symptoms). This period of time can range from 1 week to 2 months.
(C) How to administer venetoclax ± an anti-CD20 monoclonal antibody in the retreatment setting	**When retreatment with venetoclax ± anti-CD20 mAb is recommended, the decision to add anti-CD20 and the optimal treatment length should be individualized to each patient.**	Data are lacking regarding the best approach for venetoclax retreatment (venetoclax monotherapy or venetoclax combined with rituximab or obinutuzumab). In the largest series of venetoclax retreatment, venetoclax was administered as monotherapy (45.7%) or in combination with rituximab (28.2%), obinutuzumab (10.9%), ibrutinib (4.4%), or another agent (10.9%).[58] When an anti-CD20 mAb is combined with venetoclax in the retreatment setting, the majority of the panel recommends obinutuzumab with venetoclax which is initiated using a modified

		CLL14 schedule (refer to Section 5.2). Whether venetoclax should be stopped after 24 months as in the MURANO trial or until progression or intolerance is unknown.[61,62] An ongoing prospective study evaluating retreatment with venetoclax plus obinutuzumab after frontline treatment with the same regimen will provide prospective data using this strategy (ReVenG; NCT04895436).
(D) When to consider off-label pirtobrutinib in venetoclax-naïve patients after a cBTKi	**In a patient with a medical contraindication to venetoclax-based therapy, pirtobrutinib (off-label) may be considered in venetoclax-naïve patients after a cBTKi.**	Pirtobrutinib is FDA approved for patients with CLL/SLL and ≥2 prior therapies including a cBTKi and venetoclax based on the BRUIN study.[74,75] Importantly, the BRUIN study included venetoclax-naïve patients (n=154) and a *post hoc* analysis demonstrated a 2-year PFS of 83.1%. Therefore, in the setting of a medical contraindication to venetoclax-based therapy, pirtobrutinib may be considered in venetoclax-naïve patients after a cBTKi.

Table 4: MRD assessment

Topic	Consensus Statements	Justification and supporting literature
(A) MRD to guide treatment	**Currently, it is not standard practice to utilize MRD status at end of planned treatment course with venetoclax with the sole purpose of guiding treatment decisions.**	To the best of our knowledge, although MRD-guided therapies can result in an increased proportion of patients achieving uMRD4, there is currently no evidence that this translates to improved clinical outcomes.
(B) Method of MRD testing	**Immunosequencing (e.g., Adaptive ClonoSEQ) is the preferred MRD method based on its FDA approval for use in CLL/SLL and greater sensitivity ($<10^{-6}$) and reproducibility, but a baseline sequence is required. Notably, most prospective clinical trial data has relied upon flow cytometry for MRD detection. Flow cytometry has a sensitivity for uMRD $<10^{-4}$ and does not necessitate a baseline sequence, and is an acceptable approach for MRD detection.**	Immunosequencing is currently the preferred MRD method based on the availability of an FDA-cleared *in vitro* diagnostic (ClonoSEQ assay, Adaptive Biotechnologies) which renders greater sensitivity than flow cytometry. The current iwCLL definition for uMRD uses a cutoff of $<10^{-4}$ (uMRD4), and flow cytometry has adequate sensitivity for uMRD4.[3] Our panel acknowledges that detectable MRD $<10^{-4}$ is currently of unclear significance, thus may create unnecessary worry for patients. We also acknowledge that flow cytometry is more readily available at most centers.
(C) MRD testing in peripheral blood with venetoclax ± an anti-CD20 monoclonal antibody or lisocabtagene maraleucel	**Venetoclax +/- anti-CD20 monoclonal antibody:** - **We encourage MRD testing in peripheral blood at the end of the planned treatment course, as MRD serves as an important prognostic marker.** - **At present, there are insufficient data to support a prognostic or predictive role of routine MRD testing at interim timepoints or in surveillance.**	Our recommendation to measure MRD in patients with CLL/SLL receiving venetoclax-based therapy or liso-cel is based on evidence from prospective trials demonstrating correlation between end-of-treatment MRD4 status and survival outcomes.[25,26,59,77] Among previously treated patients with CLL/SLL treated with venetoclax and obinutuzumab, end-of-treatment uMRD4 is associated with longer PFS and OS.[25,26] Among previously treated patients on venetoclax with rituximab, end-of-treatment uMRD4 is associated with longer PFS.[59] Among previously treated patients receiving liso-cel, there is preliminary evidence that uMRD4 is associated with PFS.[77,78] Some of us also measure MRD at an interim timepoint in patients receiving venetoclax-based therapy. This is based on MRD kinetics data from the CLL14 trial demonstrating that some patients with detectable MRD4 at end-of-treatment had evidence of rising MRD levels, and this provides

	Lisocabtagene maraleucel: - **We encourage MRD testing in peripheral blood at day 30 and after months 3 and 6, as MRD serves as an important prognostic marker.**	information about potential emerging venetoclax resistance.[25]
(D) MRD testing with BTK inhibitors	**MRD testing is not recommended for patients receiving continuous therapy for CLL/SLL with a BTKi.**	Our recommendation against MRD testing for patients receiving continuous therapy for CLL/SLL with a BTKi is based on the lack of an association between MRD status and survival outcomes in this setting.
(E) MRD testing in bone marrow	**Bone marrow biopsies obtained solely for MRD assessment are not routinely encouraged outside of clinical trials.**	The peripheral blood and bone marrow demonstrate relatively high concordance (85-90%) to detect uMRD4 with either flow cytometry or immunosequencing.[101,104] While assessing MRD in the bone marrow compartment can identify detectable MRD4 in 10-15% of patients with uMRD4 in the peripheral blood, we find the peripheral blood MRD assessment is more practical in clinical practice. Additionally, most data linking uMRD4 and survival outcomes rely on peripheral blood MRD assessment.[25,26,59,77]

Table 5: Future directions

Future directions
Management of asymptomatic patients with high/very high-risk CLL/SLL
The S1925 trial is evaluating early fixed-duration venetoclax-obinutuzumab in asymptomatic patients with high/very high-risk CLL/SLL based on the CLL-IPI but who do not meet iwCLL criteria to initiate treatment, compared to initiation of venetoclax-obinutuzumab when traditional iwCLL criteria are met (NCT04269902). If early therapy results in an improvement in the primary endpoint of OS among high-risk patients, this would impact recommendations.[9]
Optimal sequencing of first- and second-line therapies in CLL/SLL
Prospective data directly comparing current recommended frontline treatment options are unavailable to determine a single standard initial treatment for patients with CLL/SLL. We await results from the ongoing CLL17 trial, in which previously untreated patients requiring therapy are randomized to receive ibrutinib (continuous), venetoclax-obinutuzumab (12 months), or venetoclax-ibrutinib (15 months) (NCT03406156).[31] If an OS difference is observed, or if PFS favors a time-limited regimen, this would inform treatment sequencing, e.g., whether it is best to lead with a cBTKi or venetoclax-obinutuzumab. In contrast, if a PFS difference alone favors continuous administration of ibrutinib over either time-limited regimen, this would be difficult to interpret.
Potential future impact of cBTKi/BCL2i combinations in CLL/SLL
Fixed-duration ibrutinib-venetoclax is available in Europe and the UK based on GLOW trial[32] but ibrutinib-venetoclax is not approved in the US. We await results from registrational phase 3 trials of (A) acalabrutinib-venetoclax +/- obinutuzumab vs chemoimmunotherapy (NCT03836261), and (B) zanubrutinib-sonrotoclax vs venetoclax-obinutuzumab in treatment-naïve CLL/SLL (NCT06073821), as well as the phase 3 trial of acalabrutinib-venetoclax vs venetoclax-obinutuzumab (NCT05057494). If acalabrutinib-venetoclax or zanubrutinib-sonrotoclax are approved for US patients with CLL/SLL, this would raise new questions regarding optimal second-line treatment after a fixed-duration, frontline cBTKi/BCL2i regimen.
Novel therapies in CLL/SLL
Novel investigational therapeutic agents currently under development for patients with CLL/SLL include, among others, next-generation covalent and noncovalent BTK inhibitors and BCL2 inhibitors, as well as BTK degraders and CD20xCD3 bispecific antibodies (clinicaltrials.gov). Additionally, while the current available data do not support use of a triplet regimen in CLL/SLL (i.e., Ven-O combined with ibrutinib [IVO], acalabrutinib [AVO], or zanubrutinib [BOVen]), we await results from long-term follow-up of the CLL13 trial (Ven-O vs IV vs IVO).[26]
MRD-guided therapy
Measurement of MRD provides prognostic information in patients with CLL/SLL receiving venetoclax-based therapy or liso-cel. However, to the best of our knowledge, there is no evidence that MRD-based treatment results in improved clinical outcomes. Many therapeutic trials in CLL/SLL incorporate MRD-based treatment decisions. While these data might inform use of MRD in the routine care of patients with CLL/SLL, we are not aware of any studies designed to establish whether a patient's clinical outcome is better because MRD was used to guide their care. Future trial designs could incorporate randomization to an MRD-based treatment decision vs standard of care.
Role of resistance mutation testing in routine clinical care
We await additional follow-up of patients receiving covalent and noncovalent BTK inhibitors with subsequent progression. These data might reveal differences in the pattern of resistance mutations with different BTK inhibitors, and correlation between specific resistance mutations and clinical

outcomes on present and subsequent therapies might ultimately inform subsequent treatment selection and sequencing.

Consensus Recommendations from the 2024 LRF Workshop on Treatment Selection and Sequencing in Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

Decision to initiate therapy
Refer to **Section 1**

Pretreatment assessments
Refer to **Table 1**

Selection of initial therapy

Frontline therapeutic options (Section 2)
Selection of initial therapy for each patient (Section 4)
When to choose a covalent BTK inhibitor or venetoclax-obinutuzumab **(Figure 1)**
Co-morbidities / concomitant medications and treatment selection **(Table 2)**

Second-line therapy after covalent BTK inhibitor
Refer to **Section 5**
Graphical summary **(Figure 2A)**

Second-line therapy after venetoclax-obinutuzumab
Refer to **Section 6**
Graphical summary **(Figure 2B)**

Second-line therapy after other therapies
Refer to **Section 7**

Treatment after ≥2 therapies including venetoclax and a covalent BTK inhibitor
Refer to **Section 8**
Graphical summary **(Figure 2A/2B)**

Clinical trial participation
Refer to **Section 9**

MRD assessment
Refer to **Section 10, Table 4**

Resistance mutations
Refer to **Section 11**

Special situations guidance (Table 3)

Figure 1

A

Patient preference is often the most important factor

Key features of acalabrutinib or zanubrutinib

1. Therapy until progression or intolerance
2. Only oral therapy
3. Limited visits/laboratory monitoring

Key features of venetoclax and obinutuzumab:

1. Time-limited therapy
2. Includes intravenous therapy (obinutuzumab)
3. Frequent visits/labs over the first 8 weeks

B

Strongly recommend against acalabrutinib or zanubrutinib if:

1. Concomitant dual antiplatelet therapy (check with cardiologist if DAPT is necessary)
2. Concomitant warfarin (check if non-warfarin anticoagulation is acceptable)
3. History of major bleeding with ongoing risk
4. History of ventricular arrhythmia with ongoing risk

C

Influences toward acalabrutinib or zanubrutinib

1. Presence of a 17p deletion by FISH or a *TP53* mutation by NGS

Influences toward venetoclax and obinutuzumab:

1. Concomitant single antiplatelet therapy
2. Concomitant anticoagulation (non-warfarin)
3. History of atrial fibrillation or flutter

While these factors influence our treatment selection,
all factors should be taken into account, and either therapeutic approach is reasonable

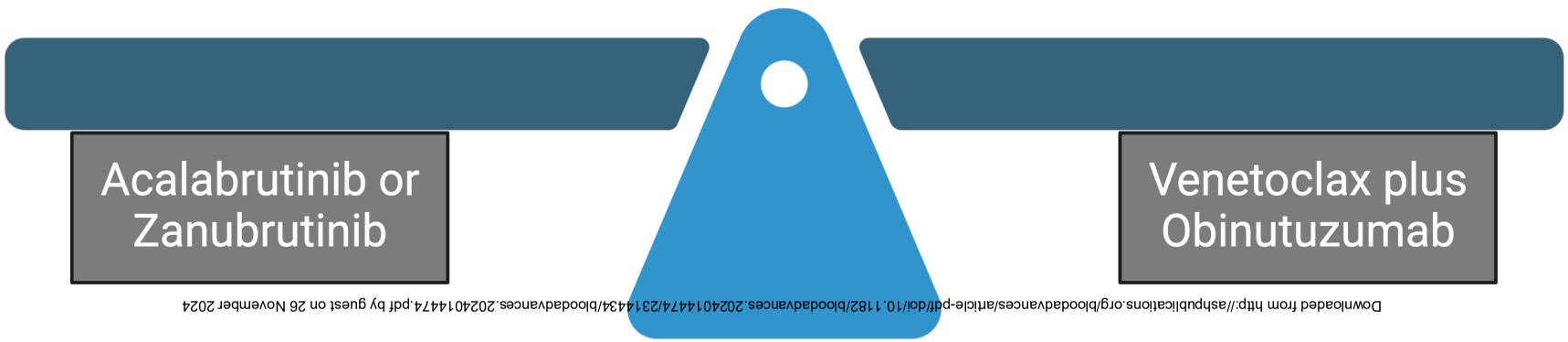

Figure 2

Figure 2A: Treatment algorithm for patients with CLL or SLL treated with initial covalent BTK inhibitor therapy

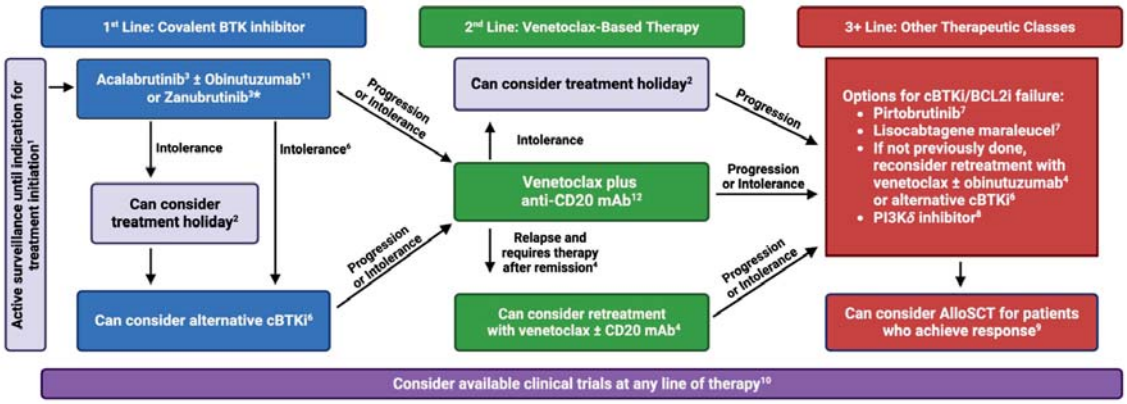

Figure 2B: Treatment algorithm for patients with CLL or SLL treated with initial venetoclax-obinutuzumab therapy