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Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma, Version 2.2026

Featured Updates to the NCCN Guidelines

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Abstract

Bruton tyrosine kinase inhibitors (BTKis) and BCL2 inhibitor (BCL2i)–containing regimens significantly improve survival outcomes in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Results from randomized clinical trials have demonstrated that time-limited treatment with BCL2i-containing regimens resulted in higher rates of undetectable measurable residual disease (uMRD) than BTKi monotherapy or chemoimmunotherapy (CIT). Pirtobrutinib (a noncovalent BTKi) and lisocabtagene maraleucel (CD19-directed CAR T-cell therapy) are newer options for relapsed or refractory disease after prior therapy with BTKi and BCL2i-contining regimens. Histologic transformation of CLL/SLL to diffuse large B-cell lymphoma (Richter transformation) is associated with a poor prognosis. Molecular analysis to determine whether there is clonal relationship between CLL/SLL and transformed diffuse large B-cell lymphoma is useful to select an appropriate treatment option. These NCCN Guideline Insights highlight significant updates to the NCCN Guidelines for the treatment of CLL/SLL and Richter transformation.

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First-Line Therapy for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Measurable Residual Disease Assessment

Measurable residual disease (MRD) is a highly sensitive indicator of disease burden in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and assessment of MRD as part of response evaluation is incorporated into some clinical trials.

MRD detection can be performed using different methods with associated sensitivities, using cells obtained from either blood or bone marrow. A commercial next-generation sequencing (NGS)–based assay was reported to achieve a limit of CLL detection down to $\leq 10^{-6}$ (MRD6), and currently is the only assay in the United States with FDA regulatory clearance.[1–4] NGS-based assays require collection of a pretreatment sample. Multicolor (≥4) flow cytometry and allele-specific oligonucleotide PCR (ASO-PCR) are the 2 other methods used to detect MRD at the level of $\leq 10^{-4}$ (MRD4) or $\leq 10^{-5}$ (MRD5), and have significantly more supporting data from clinical trials. Flow cytometry methodology was standardized by the European Research Initiative on CLL (ERIC) and is the most widely used approach due to its extensive availability and reliable detection sensitivity down to MRD5; it also does not require a pretreatment sample for analysis.[5] ASO-PCR is less widely used because it is expensive, requires a pretreatment sample, and is more labor-intensive.[6]

Consensus recommendations on MRD determination methodology, assay requirements, tissue selection (blood vs bone marrow), and the use of MRD in clinical trials have been published.[7,8] Few clinical trials have evaluated MRD-guided treatment protocols to determine treatment duration.[9–11] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL recommend serial MRD evaluations every 3 to 6 months during active treatment (using either flow cytometry [MRD flow]

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The full and most current version of these NCCN Guidelines is available at NCCN.org.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN CATEGORIES OF PREFERENCE

Preferred: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

These NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

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or NGS assay with a sensitivity for the detection of at least 10^{-4} CLL cells in blood or bone marrow), as outlined in the published trial protocols supporting MRD-guided treatment options (Figures 1 and 2). NGS-based clonality testing for MRD assessment should be considered if MRD-guided treatment is planned and MRD flow is not being used for MRD assessment. It should be noted that administration of CD20 monoclonal antibody (mAb) within the prior 3 months can lead to a false undetectable MRD4 (uMRD4) status in blood due to B-cell depletion when assessing MRD.[12,13]

MEASURABLE RESIDUAL DISEASE (MRD) ASSESSMENT

- **Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of time-limited treatment is an important predictor of efficacy.[a-e]**
- **Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and six-color flow cytometry (MRD flow) are the two validated methods used for the detection of MRD at the level of 10^{-4} to 10^{-5}.[f,g] Next-generation sequencing (NGS)-based assays have been shown to be more sensitive, thus allowing for the detection of MRD at the level of 10^{-6}.[h-j]**
- **MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method.**
- **For MRD-guided treatment, serial MRD evaluations using either flow cytometry (MRD flow) or NGS with a limit of detection (sensitivity) of at least 10^{-4} CLL cells in blood or bone marrow may be performed every 3 to 6 months during active treatment as directed in the published trial results that support MRD-guided treatment regimens. See the publications for details on MRD assessments and management, including criteria for treatment discontinuation (CSLL-E 2 of 2).**
- **Either flow cytometry (MRD flow) or NGS are acceptable assays as long as the limit of detection (sensitivity) is achieved.**
- **When assessing MRD in blood, be aware that anti-CD20 monoclonal antibody administration within the prior 3 months can lead to false undetectable MRD (uMRD) status, particularly in blood.**

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CSLL-E 1 OF 2

Figure 1. CSLL-E 1 of 2. NCCN Clinical Practice Guidelines in Oncology for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2026.

MEASURABLE RESIDUAL DISEASE (MRD) ASSESSMENT

Table 1: MRD-guided treatment regimens

Trial	First-line Therapy	Regimen
FLAIR[k]	CLL/SLL without del(17p) or *TP53* mutation	• Venetoclax/Ibrutinib[n] (category 1; other recommended)
SEQUOIA (Arm D)[l]	CLL/SLL without del(17p) or *TP53* mutation	• Venetoclax/Zanubrutinib[o] (category 2A; useful in certain circumstances)
	CLL/SLL with del(17p) or *TP53* mutation	• Venetoclax/Zanubrutinib[o] (category 2A; preferred)
Phase II study[m]	CLL/SLL with del(17p) or *TP53* mutation	• Venetoclax/Acalabrutinib + Obinutuzumab[p] (category 2A; preferred)

[k] Munir T, Girvan S, Cairns DA, et al. Measurable residual disease-guided therapy for chronic lymphocytic leukemia. N Engl J Med 2025:Online ahead of print.
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[m] Davids MS, Ryan CE, Lampson BL, et al. Phase II study of acalabrutinib, venetoclax, and obinutuzumab in a treatment-naive chronic lymphocytic leukemia population enriched for high-risk disease. J Clin Oncol 2025;43:788-799.
[n] The duration of combined ibrutinib + venetoclax was determined based on serial MRD monitoring and treatment discontinuation in patients meeting with the uMRD-guided stopping criteria.
[o] Discontinuation of treatment (venetoclax after a minimum of 12 cycles or zanubrutinib after a minimum of 27 cycles) was allowed in patients meeting with the uMRD-guided stopping criteria.
[p] Patients could discontinue treatment if CR with uMRD in the bone marrow was achieved at the start of cycle 16.

CSLL-E 2 OF 2

Figure 2. CSLL-E 2 of 2. NCCN Clinical Practice Guidelines in Oncology for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2026.

BCL2i Inhibitor–Containing Regimens

Several randomized clinical trials demonstrated that time-limited treatment (fixed-duration or MRD-guided) with BCL2 inhibitor (BCL2i)–containing regimens (venetoclax + CD20 mAb or venetoclax/covalent Bruton tyrosine kinase inhibitor [cBTKi] with or without CD20 mAb) resulted in higher rates of uMRD4 or uMRD6 in blood or bone marrow compared with BTKi monotherapy or CIT (Table 1). uMRD4 after end of treatment (EOT) with venetoclax + obinutuzumab is also an independent predictor of longer progression-free survival (PFS) among patients with previously untreated as well as relapsed or refractory CLL.[14,15]

Fixed-Duration Regimens

Ibrutinib/Venetoclax

In the phase III randomized GLOW study, fixed-duration treatment with ibrutinib/venetoclax (ibrutinib × 3 cycles followed by 12 cycles of combined ibrutinib/venetoclax) resulted in higher rate of uMRD4 at 3 months after EOT (EOT+3) across all subgroups, including del(11q) and immunoglobulin heavy chain variable region (IGHV)–unmutated CLL.[16,17] The rate of uMRD5 was also higher with ibrutinib/venetoclax (45% in blood; 40% in bone marrow) compared with chlorambucil + obinutuzumab (22% and 6%, respectively). After a median follow-up of 64 months, a PFS benefit was observed, particularly in patients with IGHV-unmutated CLL who achieved uMRD4 at EOT+3 (48-month PFS, 67% vs 40% for those with detectable MRD). PFS rates at 48 months after EOT were also higher with ibrutinib/venetoclax among patients with IGHV-mutated CLL (≥84%). independent of MRD status at EOT+3.[17]

In the GLOW trial, fixed-duration treatment with ibrutinib/venetoclax was associated with significantly longer PFS compared with chlorambucil + obinutuzumab. The 64-month follow-up also demonstrated an overall survival (OS) benefit for ibrutinib/venetoclax over chlorambucil + obinutuzumab.[16,17] The estimated PFS rate for patients with uMRD4 in the bone marrow at 12 months after EOT (EOT+12) was 96% for ibrutinib/venetoclax versus 83% for chlorambucil + obinutuzumab.[16] However, in this study, ibrutinib/venetoclax was associated with significant toxicity. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 76% of patients, with atrial fibrillation (any grade) reported in 14% and treatment-related deaths in 7% of patients.[18] Cardiac or sudden deaths during treatment occurred in patients with a Cumulative Illness Rating Scale (CIRS) score of ≥10 or an ECOG performance status (PS) of 2 and those with a history of hypertension, cardiovascular disease, and/or diabetes. This increase in toxicity may be related to the advanced age of patients enrolled in the study.

Fixed-duration treatment with ibrutinib/venetoclax also resulted in higher rates of uMRD4 (blood) at EOT compared with ibrutinib in the CLL17 trial (47% vs 0%, respectively).[19] This trial established that ibrutinib/venetoclax and venetoclax + obinutuzumab are noninferior to continuous treatment with ibrutinib in terms of 3-year PFS (79% and 81%, respectively).

Ibrutinib/venetoclax is not FDA-approved for the treatment of CLL/SLL. Based on the safety profile reported in the GLOW trial (increased risk for cardiovascular events and infections, particularly in older patients with comorbidities) and the absence of data from randomized studies comparing this regimen with approved targeted therapies for first-line therapy (other than ibrutinib), the panel

Table 1. uMRD Rates With Time-Limited BCL2i-Containing Regimens in Treatment-Naïve CLL/SLL

Trial	Regimen	Patients n	Patient Characteristics	Median Follow-Up	uMRD ($\leq 10^{-4}$; uMRD4)	PFS	MRD Detection
GLOW (phase III; fixed-duration)[16]	Ibrutinib/ Venetoclax	106	Age ≥65 y or <65 y who also had CIRS >6 or CrCl <70 mL/min	34 mo	EOT+3 (BM): 67% among patients with a CR; 64% among patients with a PR	EOT +12: 96% (uMRD4); 93% (dMRD)	NGS
	Chlorambucil + obinutuzumab	105			EOT+3 (BM): 31% among patients with a CR; 21% among patients with a PR	EOT +12: 83% (uMRD4); 59% (dMRD)	
FLAIR (phase III; MRD-guided)[9,a]	Ibrutinib	263	Median age, 62 y (>65 y, 31%) [without del(17p)]	62 mo	60 mo: 4% (blood); 0% (BM)	5-y, 79%	MRD flow
	Ibrutinib/ Venetoclax	260			60 mo: 93% (blood); 72% (BM)	5-y, 94%	
	FCR	263			60 mo: 69% (blood); 55% (BM)	5-y, 58%	
CAPTIVATE (phase II; fixed-duration)[21]	Ibrutinib/ Venetoclax	159	Age ≤70 y; ECOG PS 0–1	69 mo	Cycle 7: 54% (blood); EOT: 69% (blood and BM)	5.5-y, 66%; [75% uMRD4. 47% dMRD]	MRD flow
AMPLIFY (phase III; fixed-duration)[22]	Acalabrutinib/ Venetoclax	291	Median age, 61 y [without del(17p) or *TP53* mutation])	41 mo	EOT: 45% (blood); EOT+3: 38% (blood)	36-mo, 77%	MRD flow
	AVO	286			EOT: 95% (blood); EOT+3: 94% (blood)	36-mo, 83%	
	FCR or BR	290			EOT: 73% (blood); EOT+3: 78% (blood)	36-mo, 67%	
Phase II (MRD-guided)[10,b]	AVO	72 (n=45, *TP53* aberration)	Age ≥18 y; ECOG PS 0–1	55 mo	Cycle 16 (BM): 78% (71% for those with *TP53* aberration) Cycle 16 (blood): 83% (82% for those with *TP53* aberration)	4-y, 70% (*TP53*) 4-y, 96% (*TP53* wild-type)	NGS; MRD flow
SEQUOIA Arm D (phase III; MRD-guided)[11,c]	Zanubrutinib/ Venetoclax (nonrandomized cohort)	66 (*TP53* aberration)	Age ≥65 y OR unsuitable for FCR (CIRS >6; CrCl <70 mL/min or a history of severe/multiple infections within 2 y);	39 mo	59% (blood)	24-mo, 94%	MRD flow
		47 (without *TP53* aberration)		30 mo	60% (blood)	24-mo, 89%	

Abbreviations: AVO, acalabrutinib/venetoclax/obinutuzumab; BCL2i, BCL2 inhibitor; BM, bone marrow; BR, bendamustine/rituximab; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CIRS, Cumulative Illness Rating Scale; CR, complete remission; CrCl, creatinine clearance; dMRD, detectable MRD (>10^{-4}); EOT, end of treatment; EOT+3, 3 months after EOT; EOT+12, 12 months after EOT; FCR, fludarabine/cyclophosphamide/rituximab; MRD, measurable residual disease; MRD flow, MRD evaluations using flow cytometry; NGS, next-generation sequencing; uMRD, undetectable MRD; uMRD4, MRD at the level of $\leq 10^{-4}$; PFS, progression-free survival; PR, partial response; PS, performance score.

[a] Duration of ibrutinib/venetoclax was determined based on serial MRD monitoring and treatment discontinuation upon meeting uMRD4-guided stopping criteria.

[b] Treatment could be discontinued in patients achieving CR with BM uMRD4 at cycle 16.

[c] Treatment discontinuation (venetoclax after ≥12 cycles or zanubrutinib after ≥27 cycles) was permitted in patients meeting uMRD4-guided stopping criteria.

consensus was to include ibrutinib/venetoclax (fixed-duration treatment) as a category 1 recommendation under other recommended regimens for CLL without del(17p)/*TP53* mutation (Figure 3).

Patients with del(17p) CLL were not eligible for enrollment in the GLOW study. In the CAPTIVATE study (n=159; 27 with del(17p) and/or *TP53* mutation), fixed-duration treatment with ibrutinib/venetoclax (ibrutinib for 3 cycles followed by 12 cycles of combined venetoclax + ibrutinib) resulted in high rates of uMRD4 across all subgroups, including del(17p) and/or *TP53*-mutated, del(11q), and IGHV-unmutated CLL.[20,21] In the fixed-duration treatment cohort, uMRD4 rates were 83% in blood and 45% in bone marrow for patients with del(17p) and/or *TP53* mutation. Among patients with IGHV-unmutated CLL, uMRD4 rates were higher (88% in blood; 73% in bone marrow) compared with IGHV-mutated CLL (72% in blood; 60% in bone marrow). Despite this, the 5.5-year PFS rate was higher in patients with IGHV-mutated CLL than in those with IGHV-unmutated CLL (79% and 55% respectively).[20,21] The 5.5-year PFS rate was also higher in patients with uMRD4 (blood) at EOT than in those with detectable MRD at EOT (75% vs 47%).[21] Among patients with del(17p)/*TP53* mutation, the estimated 5.5-year PFS rate with fixed-duration ibrutinib/venetoclax was 36%.[21]

Based on the results of the CAPTIVATE study, ibrutinib/venetoclax (fixed-duration) is included as an option (other recommended regimens) for CLL with del(17p)/*TP53* mutation (Figure 3).[21]

Acalabrutinib/Venetoclax ± Obinutuzumab

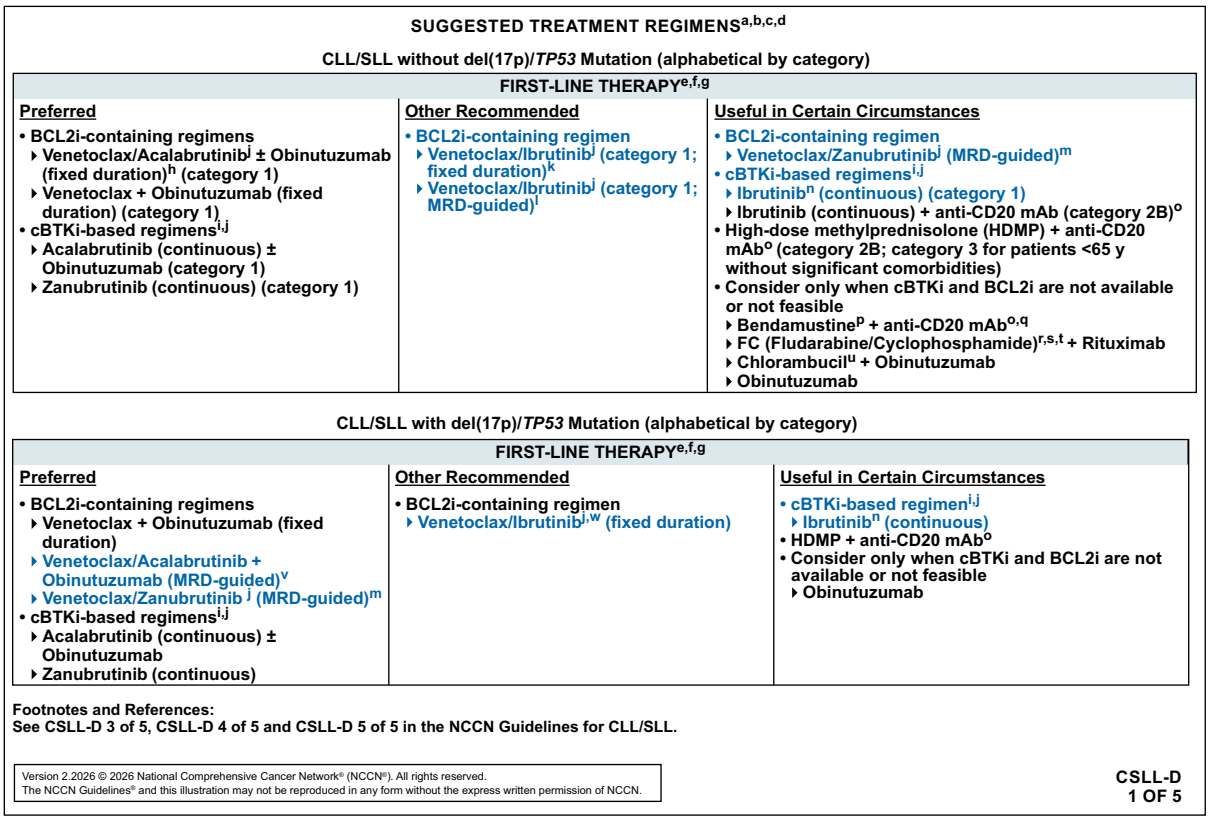
Among patients in the AMPLIFY trial with available MRD measurements at designated timepoints, uMRD4 rates in blood at EOT and at EOT+3 were also higher after fixed-duration treatment with acalabrutinib/venetoclax + obinutuzumab (AVO; 95% and 94%, respectively) compared with CIT (73% and 78%, respectively).[22] The corresponding uMRD4 rates in blood were 45% and 38%, respectively, for acalabrutinib/venetoclax, suggesting that the addition of obinutuzumab increases the uMRD4 rate. However, the lower uMRD4 rate did not correspond to a lower PFS rate with acalabrutinib/venetoclax, and longer follow-up is needed to confirm these findings. Acalabrutinib was administered during cycles 1 to 14 and venetoclax was administered from cycles 3 to 14. In the AVO arm, obinutuzumab (1,000 mg intravenously) was administered during cycles 2 to 7 (day 1).

Fixed-duration treatment with acalabrutinib/venetoclax ± obinutuzumab is included as a preferred treatment option with a category 1 recommendation for CLL/SLL without del(17p)/*TP53* mutation (Figure 3).

MRD-Guided Regimens

Ibrutinib/Venetoclax

MRD-guided treatment with ibrutinib/venetoclax was evaluated in the FLAIR study, which randomly assigned 263 patients to ibrutinib monotherapy, 260 to ibrutinib/venetoclax, and 263 to fludarabine/cyclophosphamide/rituximab (FCR).[9] In the ibrutinib/



SUGGESTED TREATMENT REGIMENS[a,b,c,d]

CLL/SLL without del(17p)/*TP53* Mutation (alphabetical by category)

FIRST-LINE THERAPY[e,f,g]

Preferred	Other Recommended	Useful in Certain Circumstances
• BCL2i-containing regimens ▸ Venetoclax/Acalabrutinib[j] ± Obinutuzumab (fixed duration)[h] (category 1) ▸ Venetoclax + Obinutuzumab (fixed duration) (category 1) • cBTKi-based regimens[i,j] ▸ Acalabrutinib (continuous) ± Obinutuzumab (category 1) ▸ Zanubrutinib (continuous) (category 1)	• BCL2i-containing regimen ▸ Venetoclax/Ibrutinib[j] (category 1; fixed duration)[k] ▸ Venetoclax/Ibrutinib[j] (category 1; MRD-guided)[l]	• BCL2i-containing regimen ▸ Venetoclax/Zanubrutinib[j] (MRD-guided)[m] • cBTKi-based regimens[i,j] ▸ Ibrutinib[n] (continuous) (category 1) ▸ Ibrutinib (continuous) + anti-CD20 mAb (category 2B)[o] • High-dose methylprednisolone (HDMP) + anti-CD20 mAb[o] (category 2B; category 3 for patients <65 y without significant comorbidities) • Consider only when cBTKi and BCL2i are not available or not feasible ▸ Bendamustine[p] + anti-CD20 mAb[o,q] ▸ FC (Fludarabine/Cyclophosphamide)[r,s,t] + Rituximab ▸ Chlorambucil[u] + Obinutuzumab ▸ Obinutuzumab

CLL/SLL with del(17p)/*TP53* Mutation (alphabetical by category)

FIRST-LINE THERAPY[e,f,g]

Preferred	Other Recommended	Useful in Certain Circumstances
• BCL2i-containing regimens ▸ Venetoclax + Obinutuzumab (fixed duration) ▸ Venetoclax/Acalabrutinib + Obinutuzumab (MRD-guided)[v] ▸ Venetoclax/Zanubrutinib [j] (MRD-guided)[m] • cBTKi-based regimens[i,j] ▸ Acalabrutinib (continuous) ± Obinutuzumab ▸ Zanubrutinib (continuous)	• BCL2i-containing regimen ▸ Venetoclax/Ibrutinib[j,w] (fixed duration)	• cBTKi-based regimen[i,j] ▸ Ibrutinib[n] (continuous) • HDMP + anti-CD20 mAb[o] • Consider only when cBTKi and BCL2i are not available or not feasible ▸ Obinutuzumab

Footnotes and References:
See CSLL-D 3 of 5, CSLL-D 4 of 5 and CSLL-D 5 of 5 in the NCCN Guidelines for CLL/SLL.

CSLL-D 1 OF 5

Figure 3. CSLL-D 1 of 5. NCCN Clinical Practice Guidelines in Oncology for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2026.

venetoclax arm, ibrutinib was administered for 8 weeks before initiation of venetoclax, and the duration of combined ibrutinib/venetoclax was from 2 to 6 years, determined by uMRD4-guided criteria. Ibrutinib/venetoclax resulted in higher rates of uMRD4 compared with FCR and ibrutinib. With a median follow-up of 62 months, uMRD4 (bone marrow) at 60 months after randomization was observed in 72% of patients in the ibrutinib/venetoclax arm, 55% in the FCR group, and 0% in the ibrutinib-alone arm. The uMRD4 (blood) at 60 months after randomization was also higher with ibrutinib/venetoclax (93%) compared with FCR (69%) and ibrutinib-alone (4%). At 6 years after treatment initiation with ibrutinib/venetoclax, an estimated 79% of patients had discontinued therapy due to achieving uMRD4, with a higher proportion in the IGHV-unmutated group compared with the IGHV-mutated group (81% and 52%, respectively). Subgroup analysis suggested a benefit of MRD-guided treatment in patients with IGHV-unmutated CLL/SLL.[9] The FLAIR trial also identified IGHV-unmutated status as a predictor of early achievement of uMRD4 following treatment with ibrutinib/venetoclax.[23] The 5-year PFS rates with ibrutinib/venetoclax were 91% for IGHV-unmutated CLL and 88% for IGHV-mutated CLL, compared with 57% and 76%, respectively, for FCR. Large, ongoing clinical trials will help clarify the optimal duration of MRD-guided treatment with combination targeted therapy and the importance of differences in uMRD4 rates between IGHV-mutated and IGHV-unmutated CLL/SLL.

Long-term follow-up (median 62 months) showed that OS was also longer with ibrutinib/venetoclax compared with ibrutinib monotherapy in patients with IGHV-unmutated CLL/SLL; however, OS was similar between the 2 treatment groups in patients with IGHV-mutated CLL/SLL.[9]

The panel consensus also supported the inclusion of ibrutinib/venetoclax (MRD-guided treatment; other recommended regimen) as a category 1 recommendation for CLL/SLL without del(17p)/TP53 mutation based on results of the FLAIR trial (Figure 3).

Acalabrutinib/Venetoclax + Obinutuzumab

A phase II single-center study investigated MRD-guided treatment with AVO in patients with previously untreated CLL/SLL (n=72; 45 patients with *TP53* aberrations).[10] Acalabrutinib was administered first, followed by acalabrutinib + obinutuzumab in cycles 2 and 3, then AVO in cycles 4 to 7, and finally and acalabrutinib/venetoclax in cycles 8 to 15. Patients could discontinue treatment if they achieved a complete response (CR) with uMRD4 (bone marrow) at the start of cycle 16. The CR with uMRD4 (bone marrow) rate was 42% in both the overall study population and in patients with *TP53*-aberrant disease, and the uMRD4 (bone marrow) rates were 71% in the overall study population and 78% in patients with *TP53*-aberrant disease. Treatment discontinuation after achieving CR with uMRD4 (bone marrow) at the start of cycle 16 was reported in 79% of patients (58% had *TP53*-aberrant disease). A total of 42% of patients (n=30) discontinued treatment after achieving CR with uMRD4 (bone marrow) before cycle 16, and an additional 38% of patients (n=27) discontinued treatment after achieving CR with uMRD4 (bone marrow) following completion of 24 cycles. The median duration of treatment was 25 cycles.

After a median follow-up of 55 months, the 4-year PFS and OS rates were 70% and 88% respectively, for patients with *TP53* aberrations.

The panel agreed that MRD-guided treatment with AVO (category 2A; preferred) is an appropriate treatment option for patients with del(17p) or *TP53* mutation based on the results of this phase II study. (Figure 3).[10] Patients with del(17p) or *TP53* mutation were not enrolled in the AMPLIFY study, and the panel acknowledged that no data are available to support the use of acalabrutinib/venetoclax in patients with del(17p) CLL/SLL.

Zanubrutinib/Venetoclax

The SEQUOIA study evaluated MRD-guided treatment with zanubrutinib/venetoclax in the nonrandomized Arm D cohort (n=114; zanubrutinib was administered as monotherapy for 3 cycles and then combined with venetoclax for cycles 4–28).[11] The best uMRD4 (blood) rates (percentage of patients achieving uMRD4 at least once) were similar in the subgroups of patients with and without *TP53* aberrations (59% and 60%, respectively). The uMRD4 (blood) rates at the beginning of cycle 16 and 28 were 43% and 60%, respectively, for patients without *TP53* aberrations. The corresponding uMRD4 rate at cycle 16 was lower in patients with *TP53* aberrations (21%) but increased to 49% by cycle 28, suggesting that patients with *TP53* aberrations may require a longer treatment duration to achieve uMRD4 rates similar to those in patients without *TP53* aberrations. Discontinuation of treatment (venetoclax after a minimum of 12 cycles or zanubrutinib after a minimum of 27 cycles) was permitted in patients meeting the uMRD4-guided stopping criteria. The treatment discontinuation rate based on the achievement of uMRD4 criteria was 10% (most of these patients did not have *TP53* aberrations).

At a median follow-up of 31 months, zanubrutinib/venetoclax resulted in an overall response rate (ORR) of 97% (96% in patients without *TP53* aberrations) and a 24-month PFS rate of 92% (89% for patients without *TP53* aberrations). Among patients with *TP53*-aberrant disease, the ORR was 99% and the 24-month PFS rate was 94%. Discontinuation of treatment was permitted in patients meeting the uMRD4 achievement criteria. Zanubrutinib was given until disease progression in patients not meeting the uMRD4 criteria.

Zanubrutinib/venetoclax is included in the NCCN Guidelines with a category 2A recommendation (useful in certain circumstances for CLL/SLL without del(17p) or *TP53* mutation; preferred treatment option for CLL/SLL with del(17p) or *TP53* mutation) (Figure 3). Given the favorable toxicity profile of zanubrutinib/venetoclax, MRD-guided treatment with this combination may be an appropriate option for patients who are intolerant to MRD-guided treatment with ibrutinib/venetoclax.

BTKi-Based Regimens

Continuous treatment with BTKi monotherapy does not typically result in uMRD4, but the use of cBTKi in combination with CD20 mAb results in higher rates of uMRD4 compared with monotherapy.[24–28] In the E1912 phase III randomized trial comparing FCR versus ibrutinib + rituximab, there was not significant difference in PFS among patients randomized to ibrutinib + rituximab based on uMRD4 status.[25] However, PFS was significantly longer in patients with MRD levels $<10^{-1}$ compared with those with MRD levels $>10^{-1}$, and continuous treatment with ibrutinib was necessary to maintain treatment efficacy. The prognostic value of uMRD4 has not been confirmed in the context of continuous BTKi monotherapy or in combination with CD20 mAb.

Given the inclusion of ibrutinib/venetoclax (fixed-duration or MRD-guided) as an option for first-line therapy (other recommended regimens), along with randomized clinical trials demonstrating a more favorable toxicity profile for acalabrutinib and zanubrutinib (vs ibrutinib),[29,30] the panel acknowledged that continuous treatment with ibrutinib monotherapy would no longer be a preferred first-line therapy option for the vast majority of patients. A few panel members also suggested that ibrutinib monotherapy would be more appropriate for patients who are able to tolerate continuous treatment with ibrutinib and receive clinical benefit, as well as patients with intolerance to venetoclax. The panel consensus supported the continued listing of ibrutinib monotherapy (continuous treatment) with a category 1 recommendation as an option under useful in certain circumstances (Figure 3).

Chemoimmunotherapy

Multiple randomized trials have shown the superior efficacy of cBTKi-based regimens and BCL2i-containing regimens over CIT.[9,14,16,17,22,31] Therefore, the panel concluded that CIT should no longer be recommended as first-line therapy, although most acknowledged that it may be considered only when cBTKi and BCL2i are not available or when treatment with these targeted therapies is not feasible (Figure 3).

Second-Line and Subsequent Therapy for CLL/SLL

Noncovalent BTKis

The noncovalent BTKi (ncBTKi) pirtobrutinib is an effective treatment option for the management of CLL resistant to cBTKi, including in patients with *BTK* C481 mutation, and is FDA-approved for the treatment of patients with relapsed or refractory CLL/SLL. The phase III randomized BRUIN CLL-321 study evaluated pirtobrutinib (n=119) versus investigator's choice of treatment (bendamustine/rituximab [BR], n=37 or idelalisib/rituximab [IdR], n=82) in patients with CLL/SLL previously treated with cBTKi with or without prior therapy with venetoclax (all patients had received prior cBTKi, and 50% had received prior therapy with venetoclax-containing regimens; cBTKi was discontinued either due to disease progression or intolerance).[32] At a median follow-up of 17 months, pirtobrutinib resulted in significant improvement in PFS compared with BR/IdR (independent review committee [IRC]–assessed PFS was 14 months for pirtobrutinib vs 9 months for BR/IdR), and the PFS benefit was observed across all patient subgroups, including those with CLL/SLL previously treated with venetoclax-containing regimens (hazard ratio [HR], 0.54) and those who had unmutated *IGHV* (HR, 0.61), *TP53* mutation and/or del(17p) (HR, 0.59), and complex karyotype (HR, 0.37). The 18-month OS rate was 73% and 71% for pirtobrutinib and BR/IdR, respectively. The OS rate, however, was confounded by a high effective crossover rate of 76%.

Based on the results of the BRUIN CLL-321 study, the panel consensus was to include pirtobrutinib as a preferred treatment option with a category 1 recommendation (irrespective of del[17p]/*TP53* mutation) for patients with intolerance to prior cBTKi, those with cBTKi-resistant disease, and for patients with relapsed or refractory disease after prior therapy with BTKi-based regimens and venetoclax-containing regimens (Figure 4).

CAR T-Cell Therapy

Lisocabtagene maraleucel (liso-cel) is a one-time infusion that does not require continuous treatment and is approved for relapsed or refractory CLL/SLL after at least 2 prior lines of therapy, including a BTKi and a BCL2i (venetoclax), based on the results of the TRANSCEND CLL 004 study.[33] Results from the combination cohort of the TRANSCEND CLL 004 study (n=56) showed that ibrutinib combined with liso-cel also resulted in high ORR (86%; 45% CR) and uMRD4 rate (86% in blood and 84% in bone marrow).[34] The median duration of response for CR was not reached. The median PFS and OS were 31 months and not reached, respectively. Liso-cel + ibrutinib was associated with lower incidences of grade ≥3 cytokine release syndrome (CRS; 4% vs 8%) and neurologic toxicity (11% vs 19%) compared with liso-cel monotherapy.[34] Ibrutinib-related TEAEs including hypertension and atrial fibrillation were observed in 7% and 2% of patients, respectively.

Liso-cel ± ibrutinib is included as a preferred option for relapsed or refractory disease after prior therapy with BTKi-based regimens and venetoclax-containing regimens, irrespective of del(17p)/*TP53* mutation (Figure 4).

Richter Transformation

Histologic transformation of CLL/SLL to diffuse large B-cell lymphoma (DLBCL; also known as Richter transformation) has a poor prognosis and only moderate response rates to CIT, with a median survival of 5 to 12 months from diagnosis. However, median survival is significantly better among patients with previously untreated CLL/SLL.[35–39]

Richter transformation can either be clonally related (78%) or clonally unrelated (22%) to underlying CLL/SLL.[36,39–45] Most patients with clonally related Richter transformation carry IGHV-unmutated disease and previously treated CLL/SLL.[40,45] Clonally unrelated Richter transformation is DLBCL that is more commonly seen in previously untreated CLL/SLL and, at least in one study, was found to harbor mutations typically associated with clonally related Richter transformation—such as *TP53*, *MYC*, *ATM*, and *NOTCH1*—in the absence of mutations frequently observed in de novo DLBCL.[43] The prevalence of *TP53* mutation, however, was significantly lower in clonally unrelated Richter transformation (23% vs 60%).[41] Although clonally related Richter transformation has inferior OS compared with clonally unrelated Richter transformation,[39,41–45] clonal relatedness has not been established as an independent predictor of clinical outcomes in multivariate analysis.[46] Clonal relatedness retained its prognostic significance for OS (along with *TP53* mutation status, International Prognostic Index, and double-hit status of DLBCL) in one series (n=58)[45]; however, in another series (n=86), clonal relatedness lost its prognostic significance in multivariate analysis, and only the absence of *TP53* aberrations was associated with a significant survival advantage.[41] Another series also reported older age, elevated lactate dehydrogenase (LDH), Richter transformation after previously treated CLL/SLL, and complex karyotype as independent predictors of shorter OS in multivariate analysis.[39]

Whole-body PET/CT scan is recommended to identify the optimal site for nodal biopsy, and biopsies should be directed to

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with or without del(17p)/*TP53* Mutation
(alphabetical by category)

SECOND-LINE OR SUBSEQUENT THERAPY[e,f]

Preferred	Other Recommended
• BCL2i-containing regimen[*] ▸ Venetoclax + Obinutuzumab • cBTKi-based regimens[i,j,x] ▸ Acalabrutinib (continuous) (category 1) ▸ Zanubrutinib (continuous) (category 1) • ncBTKi-based regimen: ▸ Pirtobrutinib (continuous) (category 1) (resistance or intolerance to prior cBTKi-based regimens)	• BCL2i-containing regimens[*] ▸ Venetoclax + Rituximab (category 1) ▸ Venetoclax[*] ▸ Venetoclax/Ibrutinib[j,y,z] (category 2B) • cBTKi-based regimen[i,j] ▸ Ibrutinib[n] (continuous) (category 1)

[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) or venetoclax + cBTKi is a treatment option for relapse after a period of remission. Single agent venetoclax (continuous) can also be considered a treatment option for relapse after a period of remission.

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR cBTKi-BASED AND BCL2i-CONTAINING REGIMENS[e,f]

Preferred	Other Recommended
• Chimeric antigen receptor (CAR) T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[aa] ± Ibrutinib[j] • ncBTKi-based regimen: ▸ Pirtobrutinib (continuous) (category 1) (if not previously given)	• PI3Ki-based regimens ▸ Duvelisib ▸ Idelalisib[bb] ± Rituximab • FC + Rituximab[s,t,**] • Lenalidomide[cc] ± Rituximab • Obinutuzumab • Alemtuzumab[dd] ± Rituximab (with del(17p)/*TP53* mutation) • Bendamustine[p] + Rituximab[q,**] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb[o] (category 2A with del[17p]; category 2B without del[17p])

[**] Not recommended for CLL/SLL with del(17p)/*TP53* mutation.

Footnotes and References:
See CSLL-D 3 of 5, CSLL-D 4 of 5 and CSLL-D 5 of 5 in the NCCN Guidelines for CLL/SLL.

CSLL-D 2 OF 5

Figure 4. CSLL-D 2 of 5. NCCN Clinical Practice Guidelines in Oncology for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2026.

lesions with highest standardized uptake value (SUV) on PET scan.[47–50] Biopsy of lesions with a maximum SUV ≥5 is recommended if there is high clinical suspicion or the lesion has a differentially higher uptake than the remaining disease.[51–54]

Molecular analysis is useful to determine whether there is a clonal relationship between CLL/SLL tumor cells and histologically transformed tumor cells. *IGHV* gene rearrangement studies of CLL/SLL and histologically transformed tissue are used to establish the clonal relationship between CLL/SLL and transformed DLBCL.[40,41] Comparative clonality testing for *IGHV* gene rearrangement should be performed on a previously defined CLL/SLL sample and on the biopsy specimen of the transformed tissue to establish clonal relatedness between CLL/SLL and DLBCL cells, either using a laboratory-based assay for *IGHV* clonality. However, initiation of therapy should not be delayed for clonality testing. If the clonal relation is unknown or clonality testing is not feasible, treatment as described for clonally unrelated Richter transformation should be considered in patients with previously untreated CLL/SLL.

The following sections discuss the treatment of Richter transformation in patients with previously treated CLL/SLL (clonally related or clonal relation unknown), as outlined in Figure 5.

Treatment Options

Enrollment in a clinical trial is recommended for all patients with Richter transformation to DLBCL. PET/CT scan is required for response assessment and should be interpreted using the 5-point scale (5-PS).

CIT regimens recommended for DLBCL typically result in poor outcomes.[35] Elevated platelet counts, higher hemoglobin levels, and lower beta-2 microglobulin levels and LDH levels have been identified as independent predictors of higher response rates to CIT.[35] However, the use of these prognostic variables to guide selection of the optimal CIT regimen for Richter transformation has not been established. In the absence of a suitable clinical trial, CIT regimens (mostly based on data from single-arm phase I/II studies summarized in Table 2) are used at NCCN Member Institutions.

Although published data supporting the use of non-CIT regimens in patients with Richter transformation are limited (with additional data forthcoming), given the unmet clinical need and lack of effective treatment options, the panel acknowledged that including non-CIT regimens as treatment options is reasonable for Richter transformation (Figure 6).

Immune checkpoint inhibitor (ICI)–based regimens (nivolumab or pembrolizumab ± ibrutinib, zanubrutinib + tislelizumab, venetoclax + atezolizumab + obinutuzumab), BTKis (acalabrutinib [category 2B] and pirtobrutinib) and bispecific antibodies (epcoritamab and glofitamab) are included as options for non-CIT regimens. CAR T-cell therapy (axicabtagene ciloleucel, tisagenlecleucel, and liso-cel) is an option for eligible patients who have received at least 1 prior systemic therapy regimen.

ICI-Based Regimens

Nivolumab and pembrolizumab (either as monotherapy or in combination with ibrutinib) have demonstrated activity in patients with Richter transformation in phase II clinical trials and ORR are higher when used in combination with ibrutinib.[55–59]

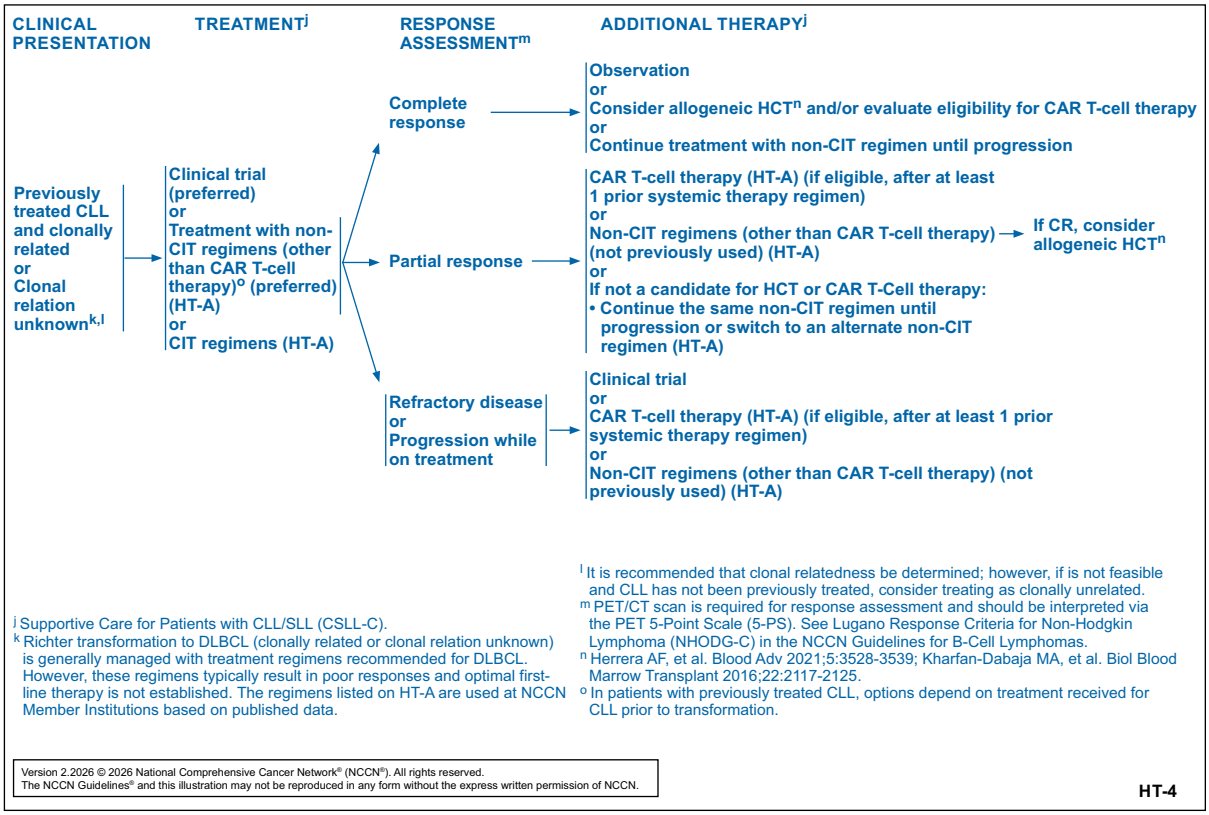


Figure 5. HT-4. NCCN Clinical Practice Guidelines in Oncology for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2026.

Table 2. Chemoimmunotherapy for Richter Transformation

Regimen	Patients, n	Median Follow-Up	ORR	Median PFS	OS
CHOP + rituximab[73]	15	69 mo	67% (7% CR)	10 mo	Median, 21 mo
CHOP + rituximab + venetoclax[74]	42	15 mo	71% (52% CR)	16 mo	Median, not reached 2-y, 63%
Dose-adjusted EPOCH + rituximab[75]	46	39 mo	39%	4 mo	Median, 6 mo
HyperCVAD + rituximab alternating with cytarabine + high-dose methotrexate[76]	30	8 mo	43% (27% CR)	—	1-y, 28%
OFA + rituximab[77]	20	9 mo	50%	—	6-mo, 53%
Modified OFA + rituximab[78]	35	26 mo	39% (7% CR)	—	Median, 7 mo 2-y, 20%

Abbreviations: CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CR, complete response; EPOCH, etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin; HyperCVAD, cyclophosphamide/vincristine/liposomal daunorubicin/dexamethasone; OFA, oxaliplatin/fludarabine/cytarabine; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

In a phase II study of 24 patients with Richter transformation, nivolumab/ibrutinib resulted in an ORR of 42%. The median duration of response (DOR) and median OS were 15 and 13 months, respectively.[58] In a subsequent phase II trial of 26 patients with Richter transformation, pembrolizumab monotherapy resulted in an ORR of 23% (8% CR and 15% partial response [PR]), with a median DOR of 3 months and a median PFS of 4 months.[59] Within this trial, an expanded analysis of 15 patients who received ibrutinib in combination with pembrolizumab demonstrated an ORR of 63% (25% CR and 38% PR), with a median DOR of 5 months and a median PFS 8 months. After a median follow-up of 50 months, the median OS for all 26 patients was 12 months, with a 2-year OS rate of 27%.

More recently, another phase II trial of 57 patients with Richter transformation (48 included in the full efficacy analysis) showed that zanubrutinib + tislelizumab was effective, achieving an ORR of 58% (19% CR).[60] After a median follow-up of 26 months, the median DOR and PFS were 17 and 10 months, respectively. The median OS was not reached, and the estimated 24-month OS rate was 63%.

In another multicenter phase II trial of 24 patients with Richter transformation, venetoclax + atezolizumab + obinutuzumab resulted in an ORR of 68%.[61] The 12-month PFS and OS rates were 43% and 64%, respectively. In the post hoc subgroup analyses, number of prior therapies for CLL/SLL and prior treatment with BTKi were predictors of OS.

BTKi Monotherapy

In a phase I/II trial of 25 patients with Richter transformation (treatment-naïve or previously treated), the cBTKi acalabrutinib resulted in an ORR of 40%, and the median PFS was 3 months.[62]

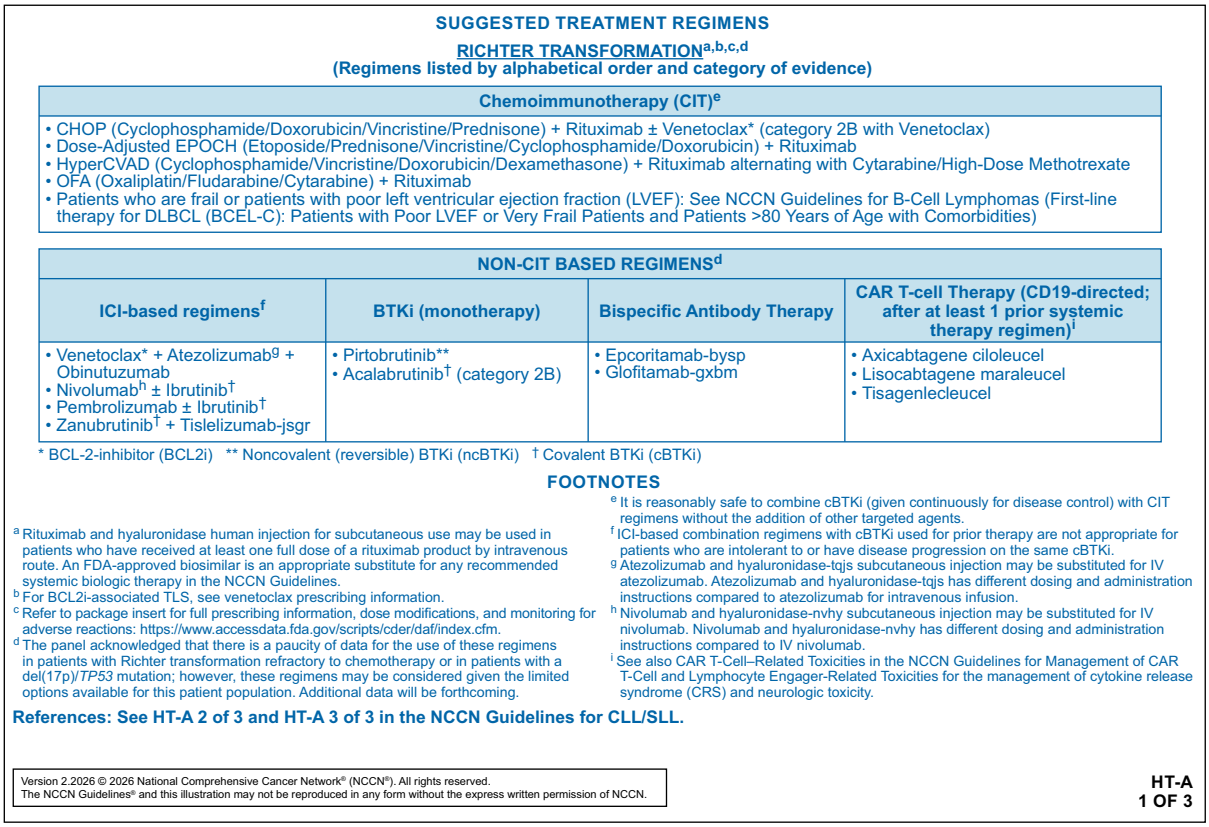


Figure 6. HT-A 1 of 3. NCCN Clinical Practice Guidelines in Oncology for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2026.

In the BRUIN phase I/II study that included 82 patients with heavily pretreated Richter transformation (including prior therapy with chemoimmunotherapy and cBTKi), the ncBTKi pirtobrutinib resulted in an ORR of 50% (13% CR and 37% PR) and was also effective as a bridge to transplant in 8 patients with ongoing response who discontinued treatment to receive hematopoietic cell transplantation (HCT).[63]

Bispecific Antibody Therapy

In the EPCORE CLL-1 trial (n=42; most patients had received ≥1 prior line of therapy with a BTKi and/or BCL2i for CLL or Richter transformation), after a median follow-up of 23 months, epcoritamab (subcutaneous CD3×CD20 bispecific antibody) resulted in an ORR of 48% (40% CR), with a median CR duration of 10 months.[64] The median PFS and OS were 3 and 13 months, respectively, for the overall study population.

In a phase I/II study of 11 patients (most with Richter transformation refractory to prior anti-CD20 mAb-containing regimens), fixed-duration treatment with glofitamab (a CD3×CD20 bispecific antibody) induced durable CRs, resulting in an ORR of 64% (46% CR).[65]

CAR T-Cell Therapy

In a real-world analysis of 30 patients with Richter transformation, at a median follow-up of 12 months, liso-cel resulted in an ORR of 76%; the median DOR, PFS, and OS were not reached.[66] The estimated 12-month rates of DOR, PFS, and OS were 77%, 54%, and 67%, respectively. Liso-cel was also well tolerated, with low incidences of grade ≥3 CRS and immune effector cell-associated neurotoxicity syndrome (ICANS).

In an international multicenter retrospective analysis (n=69; 58 patients had received prior lines of therapy with a BTKi and/or BCL2i for CLL and/or Richter transformation), CAR T-cell therapy resulted in an ORR of 63% (46% CR), with a median DOR of 28 months among patients achieving CR.[67] Axicabtagene ciloleucel, tisagenlecleucel, and liso-cel were administered in 64% (n=44), 25% (n=17), and 10% (n=7) of patients, respectively. After a median follow-up of 24 months, the median PFS and OS were 5 and 9 months, respectively, with corresponding 2-year PFS and OS rates of 29% and 38%.

HCT

In a nonrandomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher for patients who underwent allogeneic HCT (alloHCT) after achieving a CR or PR compared with those with treatment-sensitive disease who did not undergo alloHCT or who underwent alloHCT for relapsed or refractory Richter transformation (75% vs 27% and 21%, respectively; $P=.019$).[35]

In a retrospective analysis evaluating outcomes after alloHCT or autologous HCT (autoHCT) in 59 patients with Richter transformation, the 3-year estimated OS, relapse-free survival (RFS), and cumulative incidences of relapse and nonrelapse mortality rates were 36%, 27%, 47%, and 26%, respectively, for alloHCT, and 59%, 45%, 43%, and 12%, respectively, for autoHCT.[68] In a multivariate analysis, treatment-sensitive disease and reduced-intensity conditioning were found to be associated with superior RFS after alloHCT. In a Center for International Blood and Marrow Transplant Research registry study evaluating outcomes after HCT (autoHCT, n=53; alloHCT, n=118), the 3-year PFS and OS rates were 43% and 52%, respectively, for patients who underwent alloHCT, and 48% and 57%, respectively, for those who underwent auto HCT.[69]

Treatment-sensitive disease and ≤3 previous lines of therapy were associated with superior PFS and OS outcomes following alloHCT with reduced-intensity conditioning.[70] Deeper remissions at the time of transplant were associated with better survival outcomes after alloHCT.[69] AlloHCT can be considered for patients whose disease is responding to therapy, whereas autoHCT may be appropriate for those who are not candidates for alloHCT (due to age, comorbidities, or lack of a suitable donor).[35,68–72]

Richter Transformation From Previously Treated CLL/SLL (Clonally Related or Clonal Relation Unknown)

CIT or non-CIT regimens (other than CAR T-cell therapy, preferred) are included as treatment options. In patients with previously treated CLL/SLL, the choice of therapy for Richter transformation depends on the treatment received for CLL/SLL prior to transformation (Figure 5):

- ncBTKi, ICI-based combination regimens, or bispecific antibody therapy are appropriate options for transformation after prior therapy with a cBTKi and/or BCL2i-based regimens.
- cBTKi is an appropriate option for transformation after prior therapy with BCL2i-based regimens.
- ICI-based combination regimens that include a cBTKi previously used to treat CLL/SLL are not appropriate for patients who are intolerant of, or whose disease has progressed on, the same cBTKi.

AlloHCT can be considered for patients achieving a CR with any regimen. For those achieving CR with non-CIT regimens, continuation of treatment until disease progression is recommended. Observation may also be appropriate for patients achieving CR, although alloHCT is typically considered for those who are appropriate candidates.

CAR T-cell therapy or other non-CIT regimens (not previously used) are recommended for patients achieving a PR. Continuation of non-CIT regimen until disease progression or switching to an alternate non-CIT regimen is recommended in patients who are not candidates for HCT or CAR T-cell therapy.

Clinical trials, CAR T-cell therapy, or other non-CIT regimens are recommended for patients with refractory or progressive disease.

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