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Learning Objectives:

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 3.2022

Featured Updates to the NCCN Guidelines

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ABSTRACT

The treatment landscape of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has significantly evolved in recent years. Targeted therapy with Bruton's tyrosine kinase (BTK) inhibitors and BCL-2 inhibitors has emerged as an effective chemotherapy-free option for patients with previously untreated or relapsed/refractory CLL/SLL. Undetectable minimal residual disease after the end of treatment is emerging as an important predictor of progression-free and overall survival for patients treated with fixed-duration BCL-2 inhibitor-based treatment. These NCCN Guidelines Insights discuss the updates to the NCCN Guidelines for CLL/SLL specific to the use of chemotherapy-free treatment options for patients with treatment-naïve and relapsed/refractory disease.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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

FIRST-LINE THERAPY[e]		
	Preferred regimens	Other recommended regimens
Patients age ≥65 y OR Patients age <65 y with significant comorbidities (creatinine clearance [CrCl] <70 mL/min)	• Acalabrutinib[f] ± obinutuzumab (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + obinutuzumab (category 1) • Zanubrutinib[f]	• Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody[d,h,i] • Chlorambucil + obinutuzumab • Obinutuzumab • High-dose methylprednisolone (HDMP) + rituximab or obinutuzumab (category 2B) • Ibrutinib[f] + obinutuzumab (category 2B) • Chlorambucil (category 3) • Rituximab (category 3)
Patients age <65 y without significant comorbidities	Preferred regimens • Acalabrutinib[f] ± obinutuzumab (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + obinutuzumab • Zanubrutinib[f]	Other recommended regimens • Bendamustine + anti-CD20 monoclonal antibody[d,h,j] • FCR (fludarabine,[k] cyclophosphamide, rituximab)[j,l] (preferred for patients with IGHV-mutated CLL) • Ibrutinib[f] + rituximab (category 2B) • FR (fludarabine[k] + rituximab)[l,m] (category 3) • HDMP + rituximab or obinutuzumab (category 3)

See Footnotes on CSLL-D 4 of 6
See Suggested Regimens for Second-line and Subsequent Therapy for CLL/SLL without del(17p)/*TP53* mutation (2 of 6)
See Suggested Regimens for CLL/SLL with del(17p) (3 of 6)

Overview

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are characterized by progressive accumulation of leukemic cells in blood, bone marrow, and lymphoid tissues. Morphologically, these leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or prolymphocytes. In 2022, an estimated 20,160 people will be diagnosed with CLL in the United States, and an estimated 4,410 people will die of the disease.[1]

CLL and SLL are essentially different manifestations of the same disease and are managed in much the same way.[2] The major difference is that in CLL, a significant number of the abnormal lymphocytes are found circulating in blood in addition to being resident in bone marrow and lymphoid tissue, whereas in SLL, the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues and there are few (if any) abnormal lymphocytes circulating in blood.

CLL/SLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. The age cutoff of 65 years is used in most of the chemoimmunotherapy-based clinical trials, including the studies conducted by the German CLL Study Group (GCLLSG).[3] Comorbidities are frequently present in older patients, and the presence of multiple comorbidities (≥2 comorbidities) was an independent predictor of clinical outcome, independent of patients' age or disease stage.[4] In patients with indications for initiating treatment, patient age, performance status, comorbidities, and the presence or absence of del(17p) or *TP53* mutation help direct treatment planning.

These NCCN Guidelines Insights discuss the updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL specific to the use of chemotherapy-free treatment options for patients with previously untreated and relapsed/refractory disease.

First-Line Therapy

In addition to the aforementioned disease- and patient-specific factors, agents' toxicity profile and duration of treatment (continuous vs fixed duration) should also be considered for the selection of first-line therapy. Bruton's tyrosine kinase inhibitors (BTKis) are given continuously until disease progression, whereas venetoclax-based combination regimens offer a defined treatment course. Fixed duration treatment with venetoclax-based combination regimens also results in higher rates of undetectable minimal residual disease (uMRD), which is an independent predictor of improved survival. See later sections on "Minimal Residual Disease" and "Management of Adverse Events" (pages 631 and 632, respectively).

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

	SECOND-LINE AND SUBSEQUENT THERAPY[e]	
	Preferred regimens	**Other recommended regimens**
Patients age ≥65 y OR Patients age <65 y with significant comorbidities (creatinine clearance [CrCl] <70 mL/min)	• Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Zanubrutinib[f,n]	• Chlorambucil + rituximab • Duvelisib[f] • Idelalisib[f] ± rituximab[o] • Lenalidomide[p] ± rituximab • Obinutuzumab • Ofatumumab[q] • Venetoclax[f,g] • Bendamustine + rituximab[i] (category 2B) • HDMP + rituximab or obinutuzumab (category 2B) • Dose-dense rituximab (category 3)
Patients age <65 y without significant comorbidities	**Preferred regimens** • Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Zanubrutinib[f,n]	**Other recommended regimens** • Bendamustine + rituximab • Duvelisib[f] • FCR[k,l] • Idelalisib[f] ± rituximab[o] • Lenalidomide[p] ± rituximab • Obinutuzumab • Ofatumumab[q] • Venetoclax[f,g] • HDMP + rituximab or obinutuzumab (category 2B) • Alemtuzumab[r] ± rituximab (category 3) • Bendamustine, rituximab + ibrutinib[f] (category 3) • FC (fludarabine, cyclophosphamide)[k,l] + ofatumumab[q] (category 3)

See Footnotes on CSLL-D 4 of 6
See Suggested Regimens for CLL/SLL with del(17p) (3 of 6)

The efficacy data from phase III randomized clinical trials that evaluated small molecule inhibitors as first-line therapy are summarized in Table 1.

CLL/SLL Without del(17p) or *TP53* Mutation

BTK Inhibitors

Acalabrutinib and ibrutinib are the FDA-approved irreversible BTKis for the treatment of patients with previously untreated CLL/SLL.

Acalabrutinib ± obinutuzumab demonstrated superior progression-free survival (PFS) versus chlorambucil + obinutuzumab in patients with previously untreated CLL in the phase III ELEVATE-TN trial.[5] At 48 months follow-up, longer PFS (87% vs 78%) was seen with acalabrutinib + obinutuzumab compared with acalabrutinib, although the study was not planned or powered to compare the PFS benefit between the 2 acalabrutinib arms.

Ibrutinib monotherapy was approved for first-line therapy for all patients based on the results of the RESONATE-2 study that established the efficacy of ibrutinib monotherapy in patients aged ≥65 years without del(17p).[6,7] The ECOG-ACRIN cancer research group (E1912) study (age ≤70 years) and the FLAIR study (median age, 62 years; patients aged >75 years and with >20% del(17p) cells were excluded) showed that ibrutinib + rituximab was more effective than fludarabine/cyclophosphamide/rituximab (FCR) for patients without del(17p)/*TP53* mutation, especially for those with unmutated *IGHV*, indicating that ibrutinib is an appropriate option for younger patients with *IGHV*-unmutated CLL.[8,9] The results of other randomized phase III trials showed that ibrutinib + rituximab or obinutuzumab is more effective than chemoimmunotherapy for previously untreated CLL without del(17p) or *TP53* mutation in patients aged ≥65 years or in younger patients with comorbidities.[10–13] However, the addition of rituximab to ibrutinib did not result in improvement in clinical outcomes compared with ibrutinib monotherapy,[10,12] and there are no randomized clinical trials that compare ibrutinib versus ibrutinib + obinutuzumab. Therefore, standard of care with ibrutinib treatment in first-line or relapsed/refractory CLL is monotherapy.

Zanubrutinib is a highly selective/specific irreversible BTKi that is FDA-approved for the treatment of Waldenström's macroglobulinemia and relapsed/refractory mantle cell lymphoma. In the phase III SEQUOIA study, zanubrutinib resulted in higher overall response rate (ORR; 95% vs 85%) and statistically significant improvement in PFS compared with bendamustine + rituximab (BR) in patients with untreated CLL without del(17p)/*TP53* mutation (hazard ratio [HR], 0.42; $P<.0001$).[14] PFS benefit was observed in patients with del(11q) and unmutated

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by category)
Chemoimmunotherapy is not recommended since del(17p)/*TP53* mutation is associated with low response rates.

FIRST-LINE THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f] ± obinutuzumab	• Alemtuzumab[r] ± rituximab
• Ibrutinib[f]	• HDMP + rituximab
• Venetoclax[f,g] + obinutuzumab	• Obinutuzumab
• Zanubrutinib[f]	

SECOND-LINE AND SUBSEQUENT THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f,n] (category 1)	• Alemtuzumab[r] ± rituximab
• Ibrutinib[f] (category 1)	• Duvelisib[f]
• Venetoclax[f,g] + rituximab (category 1)	• HDMP + rituximab
• Venetoclax[f,g]	• Idelalisib[f] ± rituximab[o]
• Zanubrutinib[f,n]	• Lenalidomide[p] ± rituximab
	• Ofatumumab[q,s]

See Footnotes on CSLL-D 4 of 6
See Suggested Regimens for CLL/SLL without del(17p) (1 of 6)

IGHV (HR, 0.24; *P*<.0001) but not for patients with mutated *IGHV* (HR, 0.67; *P*=.0929), which may be due to the relatively short follow-up for this initial report.

BCL-2 Inhibitors

Venetoclax is the only FDA-approved BCL-2 inhibitor for the treatment of patients with CLL/SLL.

The CLL14 study established venetoclax + obinutuzumab as an effective fixed-duration chemotherapy-free first-line treatment option with significantly improved PFS compared with chlorambucil + obinutuzumab in patients aged ≥65 years or in younger patients with comorbidities (cumulative illness rating scale [CIRS] score >6 or an estimated creatinine clearance [CrCl] <70 mL/min).[15] The uMRD rate at the end of treatment (EoT) was significantly higher with venetoclax + obinutuzumab (74% vs 34%; *P*<.0001), and this combination was also associated with lower rate of conversion to MRD-positive status 1 year after treatment.[15,16]

The efficacy of venetoclax + obinutuzumab in patients aged <65 years without significant comorbidities was not established in a randomized clinical trial, although preliminary data from a more recent randomized phase III study (CLL13) suggest that first-line therapy with venetoclax + obinutuzumab may be more effective than chemoimmunotherapy (FCR or BR) in patients aged <65 years in terms of uMRD rate in blood (87% vs 52% for chemoimmunotherapy with FCR or BR; *P*<.0001) and bone marrow (73% vs 37% for chemoimmunotherapy with FCR or BR) at 15 months.[17] Based on the broad FDA approval, the panel members agreed that venetoclax + obinutuzumab is an appropriate fixed-duration chemotherapy-free treatment option for younger patients without comorbidities.

NCCN Recommendations

Preferred Regimens

Acalabrutinib ± obinutuzumab and ibrutinib are included with a category 1 recommendation and zanubrutinib is included with a category 2A recommendation for all patients with CLL without del(17p) or *TP53* mutation (CSLL-D 1 of 6, page 624).[5–8,14]

Venetoclax + obinutuzumab is included with a category 1 recommendation for patients aged ≥65 years or in younger patients with significant comorbidities.[15] The panel consensus was to include venetoclax + obinutuzumab with a category 2A recommendation for patients GED <65 years without significant comorbidities (CSLL-D 1 of 6, page 624).

Other Recommended Regimens

Ibrutinib + obinutuzumab (for patients aged ≥65 years and in younger patients with significant comorbidities)

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation

[a] See references for regimens CSLL-D 5 of 6 and CSLL-D 6 of 6.
[b] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route.
[d] Re-challenge with the same monoclonal antibody is not recommended in patients experiencing rare complications (eg, mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis). It is unclear whether re-challenge with alternative anti-CD20 antibodies poses the same risk of recurrence.
[e] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[f] See Special Considerations for the Use of Small-Molecule Inhibitors (CSLL-F).
[g] See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[h] Anti-CD20 monoclonal antibodies include: rituximab, ofatumumab, or obinutuzumab. While ofatumumab is no longer commercially available for CLL, it may be obtained for clinical use.
[i] Not recommended for frail patients.
[j] Data from the CLL10 study confirm the superiority of FCR over bendamustine + rituximab (BR) in younger patients. For patients >65 y, the outcome was similar for both regimens with less myelosuppression and infection for BR. FCR was associated with improved PFS (with a plateau in PFS beyond 10-year follow-up) in patients with mutated IGHV without del (17p)/*TP53* mutation (Thompson P, et al. Blood 2016;127:303-309).
[k] See Discussion for further information on oral fludarabine.
[l] AIHA should not preclude the use of combination therapy containing fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those where a history of fludarabine-associated AIHA is suspected.
[m] Not recommended for CLL with del(11q). Outcomes for CLL with del(11q) are better with chemoimmunotherapy containing an alkylating agent.
[n] Acalabrutinib or zanubrutinib has not been shown to be effective for ibrutinib-refractory CLL with BTK C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib or zanubrutinib without recurrence of symptoms.
[o] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or NCI CTCAE grade ≥3 neutropenia or grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).
[p] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Andritsos L, et al. J Clin Oncol 2008;26:2519-2525; Wendtner C, et al. Leuk Lymphoma 2016;57:1291-1299.
[q] While ofatumumab is no longer commercially available for CLL, it may be obtained for clinical use.
[r] While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Alemtuzumab is less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation. See Treatment and Viral Reactivation (CSLL-C 1 of 4).
[s] This is not effective in patients with lymph nodes >5 cm.

**CSLL-D
4 OF 6**

and ibrutinib + rituximab (for patients aged <65 years without significant comorbidities) are included with a category 2B recommendation (CSLL-D 1 of 6, page 624).[8,11]

CLL/SLL With del(17p) or *TP53* Mutation

There are limited data from prospective clinical studies on the efficacy of BTKis or BCL-2 inhibitors as first-line therapy in patients with del(17p)/*TP53*-mutated CLL.

Patients with del(17p) CLL were not eligible for enrollment in the RESONATE-2 study and the E1912 study.[6,8] In the RESONATE-2 study, 12 patients treated with ibrutinib had *TP53* mutation, and after 6-year follow-up the estimated 5-year PFS rate was 56% for this group of patients.[6] However, comparison between ibrutinib and chlorambucil could not be made because only 3 patients in the chlorambucil group had *TP53* mutation. In a phase II trial that included 35 treatment-naïve patients with del(17p)/*TP53* mutation (median age, 62 years), ibrutinib resulted in an ORR of 96% (29% complete response and 67% partial response), and the estimated 5-year PFS and OS were 74% and 85%, respectively.[18]

In the ELEVATE-TN study, the PFS benefit for acalabrutinib ± obinutuzumab was seen across all patient subgroups, including those with del(17p) or *TP53* mutation, but only 14% of patients had del(17p) CLL.[5] The 48-month PFS rates were 75% and 76%, respectively, for acalabrutinib + obinutuzumab and acalabrutinib monotherapy in patients with del(17p) and/or *TP53* mutation. In the CLL14 study, the PFS benefit for venetoclax + obinutuzumab was also seen across all patient subgroups including those with del(17p) or *TP53* mutation (del(17p) or mu-tated *TP53* were seen only 8% and 12% of patients, respectively).[15]

In the phase III SEQUOIA study, patients with del(17p) were not part of the randomized cohort but were enrolled only to single-agent zanubrutinib or subsequently, to the combination of zanubrutinib and venetoclax. In the prospectively enrolled nonrandomized cohort [109 patients with del(17p)/*TP53* mutated CLL], single agent zanubrutinib resulted in an ORR of 95% (3% complete response; 87% partial response).[19] After a median follow-up of 18 months, the median PFS and OS were not reached. The estimated 18-month PFS and OS rates were 89% and 95%, respectively. The best ORR and 18-month PFS rates were 98% and 89%, respectively, for patients with high del(17p) (≥20%), and were 92% and 88%, respectively, for patients with low del(17p) (>7% to <20%).

NCCN Recommendations

Enrollment in an appropriate clinical trial is recommended for patients with untreated del(17p) CLL.

Table 1. Phase III Randomized Studies of Small Molecule Inhibitor Therapy for Treatment-Naïve CLL/SLL

Trial	Regimen	Patients, n	Patient Characteristics	Median Follow-Up	ORR	PFS	OS
ELEVATE-TN [5]	**Acalabrutinib**	179 [del(17p) and/or mutated *TP53*, n=23]	Age ≥65 y or <65 y with comorbidities (CIRS >6; CrCl <70 mL/min); ECOG PS of ≤2 and adequate hematologic, hepatic, and renal function	48 mo	90% (11% CR)	78% (HR, 0.19; *P*<.0001)	88%
	Acalabrutinib + obinutuzumab	179 [del(17p) and/or mutated *TP53*, n=25]		48 mo	96% (31% CR)	87% (HR, 0.10; *P*<.0001)[a]	93%
	Chlorambucil + obinutuzumab	177 [del(17p)and/or mutated *TP53*, n=25]		48 mo	83% (13% CR)	25%	88%
RESONATE-2[7]	**Ibrutinib**	136	≥65 y [without del(17p)]	7 y	92% (34% CR)	6.5-y: 61%	6.5-y: 78%
	Chlorambucil	133	≥65 y [without del(17p)]	7 y	37%	6.5-y: 9%	NR
Alliance North American Intergroup (A041202)[12,13]	**Ibrutinib**	182	≥65 y	55 mo	93% (7% CR)	4-y: 76%	4-y: 85%
	Ibrutinib + rituximab	182	≥65 y	55 mo	94% (12% CR)	4-y: 76%	4-y: 86%
	Bendamustine + rituximab	183	≥65 y	55 mo	81% (26% CR)	4-y: 47%	4-y: 84%
E1912 study[8]	**Ibrutinib + rituximab**	354	≤70 y	34 mo	96% (17% CR)	3-y: 89%	3-y: 99%
	FCR	175	≥65 y	34 mo	81% (30% CR)	3-y: 73%	3-y: 92%
FLAIR[9]	**Ibrutinib + rituximab**	386	Median age; 62 y (34% >65 y); patients aged >75 y or with >20% del(17p) cells were excluded	53 mo	—	Median: NR	No difference in OS between the 2 arms (HR, 1.01; *P*=.956)
	FCR	385		53 mo	—	Median: 67 mo	
iLLUMINATE[11]	**Ibrutinib + obinutuzumab**	113	Age ≥65 y or <65 y with comorbidities (CIRS >6; CrCl <70 mL/min)	31 mo	88% (20% CR)	Median: NR (30-mo: 79%)	Median: NR (30-mo: 86%)
	Chlorambucil + obinutuzumab	116		31 mo	73% (8% CR)	Median: 19 mo (30-mo: 31%)	Median: NR (30-mo: 85%)
SEQUOIA[14] [without del(17p)]	**Zanubrutinib**	241 (mutated *TP53*, n=15)	Age ≥65 y OR unsuitable for treatment with FCR (CIRS >6; CrCl <70 mL/min or a history of severe or multiple infections within 2 y) Median age, 70 y	24 mo	95% (7% CR)	86% (HR, 0.42; *P*<.0001)	94%
	Bendamustine + rituximab	238 (mutated *TP53*, n=15)		24 mo	85% (15% CR)	70%	95%
SEQUOIA[19] [with del(17p)]	**Zanubrutinib** (nonrandomized cohort)	109		18 mo	95% (3% CR)	89%	95%
CLL14[15]	**Venetoclax + obinutuzumab**	216 [del(17p), n=17; deleted or mutated *TP53*, n=25]	Age ≥65 y with comorbidities (CIRS >6; CrCl >70 mL/min)	40 mo	85% (50% CR)	3-y: 82% (HR, 0.31 *P*<.0001)	Median: NR in either arm (HR, 1.03; *P* <0.92)
	Chlorambucil + obinutuzumab	216 [del(17p), n=14; deleted or mutated *TP53*, n=24]		40 mo	71% (23% CR)	3-y: 50%	

Abbreviations: CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; CR, complete response; CrCl, creatinine clearance; FCR, fludarabine/cyclophosphamide/rituximab; HR, hazard ratio; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma.
[a]HR and *P* values are for acalabrutinib + obinutuzumab vs chlorambucil + obinutuzumab. This study was not powered for the comparison between acalabrutinib + obinutuzumab vs acalabrutinib.

Given currently available data, acalabrutinib ± obinutuzumab; ibrutinib; venetoclax ± obinutuzumab; and zanubrutinib are included as preferred treatment options for first-line therapy, each with a category 2A recommendation (CSLL-D 3 of 6, page 626).[5,15,18,19]

Second-Line and Subsequent Therapy

The efficacy data (ORR, PFS, and OS) from randomized clinical trials that evaluated small molecule inhibitors for relapsed/refractory CLL/SLL are summarized in Table 2.

In addition to the aforementioned considerations for selection of first-line therapy, the type of prior first-line therapy, duration of remission, and acquired resistance to treatment are also important factors in the selection of treatment for relapsed/refractory CLL/SLL. See later section on "Management of Resistance to Small Molecule Inhibitors" (page 632).

Acalabrutinib, ibrutinib, and venetoclax ± rituximab are also approved for the treatment of relapsed/refractory

Table 2. Phase III Randomized Studies of Small Molecule Inhibitor Therapy for Relapsed/Refractory CLL/SLL

Trial	Regimen	Patients n	Patient Characteristics	Median Follow-Up	ORR	PFS	OS
ASCEND[21]	**Acalabrutinib**	155 [del(17p), n=28; mutated *TP53*, n=39]	Median age, 67–68 y with ECOG PS ≤2 and adequate hematologic, hepatic, and renal function	36 mo	83%	Median: NR 36-mo: 63% (HR, 0.29; *P*<.0001)	36-mo: 80%
	Investigator's choice (IdR or BR)	155 (IdR, n=119; BR, n=36); [del (17p), n=21; mutated *TP53*, n=34]		36 mo	85%	Median: 17 mo 36-mo: 21%	36-mo: 73%
RESONATE[22]	**Ibrutinib**	195 [del(17p), n=63; mutated *TP53*, n=79]	Median age, 67 y	74 mo	91% (11% CR)	Median: 44 mo 60-mo: 40%	Median: 68 mo
	Ofatumumab	196 [del(17p), n=64; mutated *TP53*, n=68]		74 mo		Median: 8 mo 60-mo: 3%	Median: 65 mo
ELEVATE-RR[27]	**Acalabrutinib**	268	Age ≥18 y; ECOG PS ≤2 and the presence of del(17p) and/or del(11q)	41 mo	81% (3% CR)	Median: 38 mo (for both treatment arms)	Median: NR (in either arm)
	Ibrutinib	265		41 mo	77% (4% CR)		
ALPINE[31]	**Zanubrutinib**	207 [del(17p) and/or mutated *TP53*, n=41]	Median age, 67 y; ECOG PS ≥1; relapsed/refractory disease ≥1 prior systemic therapy	15 mo	78%	12-mo: 95% (HR, 0.40; *P*=.0007)	12-mo: 97%
	Ibrutinib	208 [del(17p) and/or mutated *TP53*, n=38		15 mo	63% (1% CR)	12-mo: 84%	12-mo: 93%
MURANO[25]	**Venetoclax + rituximab**	194 [del(17p), n=46; mutated *TP53*, n=48]	Age ≥18 y; ECOG PS 0–1; relapsed/refractory disease requiring therapy and adequate bone marrow, liver, and kidney function	59 mo	92% (8% CR)	Median: 54 mo (HR, 0.19; *P*<.0001)	5-y: 82% (HR, 0.40; *P*<.0001)
	Bendamustine + rituximab	195 [del(17p), n=46; mutated *TP53*, n=51]		59 mo	72% (4% CR)	Median: 17 mo	5-y: 62%

Abbreviations: BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; CR, complete response; HR, hazard ratio; IdR, idelalisib + rituximab; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; SLL, small lymphocytic lymphoma.

CLL/SLL based on the results of phase III randomized studies (ASCEND, RESONATE, and MURANO trials, respectively).[20–25] The PFS benefit compared with chemoimmunotherapy was seen across all patient subgroups, including those with del(17p) or *TP53* mutation.

In the ASCEND study, at a median follow-up of 36 months, the median PFS was not reached and the 36-month PFS rate was 66% for patients with del(17p)/*TP53* mutation assigned to acalabrutinib.[21] The final analysis of the RESONATE study showed that the presence of del(17p)/*TP53* mutation or complex karyotype (CK) was not associated with inferior PFS outcomes to ibrutinib.[22] In an exploratory analysis that combined data from patients with del(17p) and *TP53* mutation, the median PFS was 41 months for those with del(17p) and/or *TP53* mutation versus 57 months for those without del(17p) or *TP53* mutation. Similarly, the median PFS was 41 months for patients with CK compared with 45 months for those without CK. The phase II RESONATE-17 study established the efficacy and safety of ibrutinib in patients with relapsed/refractory del(17p) CLL (n=145), demonstrating an ORR of 83% (as assessed by the independent review committee).[26] The phase III ELEVATE-RR trial demonstrated that acalabrutinib is noninferior to ibrutinib in terms of PFS and was also associated with a more favorable safety profile in patients with relapsed/refractory del(17p) CLL.[27]

In the phase III randomized MURANO study that compared venetoclax + rituximab (VenR) versus BR in patients with relapsed/refractory CLL, VenR was superior to BR with longer PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation (HR, 0.21 for del(17p); HR, 0.25 for *TP53* mutation) and uMRD at the EoT was higher for VenR (62% vs 13% for BR).[24] Venetoclax monotherapy also demonstrated efficacy in patients with relapsed/refractory del(17p) CLL, resulting in ORR of 77% (63% in patients who received prior therapy with B-cell receptor [BCR] signaling pathway inhibitors [BCRi]; ibrutinib or idelalisib).[28] The estimated 24-month PFS and OS rates were 54% and 73%, respectively, for the overall study population (50% and 55%, respectively, for patients who had received prior BCRi).

Zanubrutinib also demonstrated activity in patients with relapsed/refractory CLL.[29–31] The first interim analysis of the randomized phase III study (ALPINE) showed that zanubrutinib was more effective than ibrutinib, resulting in significantly higher ORR and longer PFS in patients with relapsed/refractory CLL/SLL.[31] The ORR was also higher for zanubrutinib (83% vs 54% for ibrutinib) in patients with del(17p)/*TP53* mutation.

PI3K inhibitors (idelalisib + rituximab [IdR] and duvelisib) also demonstrated efficacy (in terms of median PFS) in randomized phase III studies for patients with

Table 3. Adverse Events of Bruton's Tyrosine Kinase Inhibitors

	Treatment-Naïve CLL			Relapsed/Refractory CLL			
	ELEVATE-TN[5]	RESONATE-2[6]	SEQUOIA[19]	ELEVATE-RR[27]		ALPINE[31]	
Adverse Events	Acalabrutinib	Ibrutinib	Zanubrutinib	Acalabrutinib	Ibrutinib	Zanubrutinib	Ibrutinib
Most common adverse events (all grades)							
Diarrhea	40%	50%	16%	35%	46%	17%	19%
Headache	38%	NR	8%	35%	20%	NR	NR
Cough	22%	36%	NR	29%	21%	13%	6%
Fatigue	22%	36%	10%	20%	17%	NR	NR
Arthralgia	20%	26%	11%	16%	23%	9%	14%
Anemia	NR	26%	4%	22%	19%	13%	15%
Neutropenia	12%	13% (grade ≥3)	18%	21%	25%	28%	22%
Adverse events of special interest							
Atrial fibrillation/flutter							
Any grade	6%	16%	3%	9%	16%	2.5%	10%
Grade ≥3	1%	5%	<1%	5%	3%	1%	2%
Bleeding							
Any grade	42%	NR	45%	38%	51%	36%	36%
Grade ≥3	3%	NR	4%	NR	NR	3%	3%
Major bleeding							
Any grade	4%	11%	5%	NR	NR	3%	4%
Grade ≥3	3%	7%	4%	NR	NR	3%	3%
Hypertension							
Any grade	7%	23%	14%	9%	23%	17%	16%
Grade ≥3	3%	8%	6%	4%	9%	11%	11%
Infections							
Any grade	74%	26%	62%	NR	NR	60%	63%
Grade ≥3	16%	NR	16%	NR	NR	13%	18%

Abbreviations: CLL, chronic lymphocytic leukemia; NR, not reported.

relapsed/refractory CLL/SLL.[32–35] However, they were associated with increased risk of hepatotoxicity (transaminase elevations), severe diarrhea or colitis, pneumonitis, opportunistic infections, and febrile neutropenia.

NCCN Recommendations

Preferred Regimens

Acalabrutinib, ibrutinib, and VenR are included with a category 1 recommendation,[20–22,36] zanubrutinib is included with a category 2A recommendation,[31] and venetoclax monotherapy is included with a category 2A recommendation (preferred regimen for patients with del(17p) CLL) (CSLL-D 2 of 6, page 625).[28]

Other Recommended Regimens

IdR and duvelisib are included as options for relapsed/refractory CLL/SLL with a category 2A recommendation due to their toxicity profile.[32–35] Idelalisib monotherapy also demonstrated activity in relapsed/refractory SLL.[37,38] The indication for idelalisib monotherapy in relapsed/refractory SLL was withdrawn by the manufacturer because they are unable to complete the required confirmatory studies following the FDA accelerated approval. Although the panel acknowledged the change in the regulatory status of idelalisib, the panel consensus was to continue listing idelalisib monotherapy as an option for relapsed/refractory SLL, given demonstrated efficacy (CSLL-D 2 of 6, page 625).[37,38]

Special Considerations for the Use of Small Molecule Inhibitors

Minimal Residual Disease

Assessment of measurable residual disease (MRD; often referred to as minimal residual disease) emerged as a highly sensitive indicator of disease burden in patients with CLL, supporting the integration of MRD assessment

as part of response evaluation in the context of clinical trials.

MRD detection can be performed using either blood or bone marrow. A commercial next-generation DNA sequencing (NGS)–based assay has been reported to be more sensitive allowing for the detection of MRD at the level of 10^{-6} and is the only assay currently available in the United States that is cleared by FDA.[39–42] NGS-based assays require collection of a pretreatment sample. Multicolor (≥4) flow cytometry (MRD flow) and allele-specific oligonucleotide IGHV real-time quantitative polymerase chain reaction (ASO IGH RQ-PCR) are the 2 other methods used for the detection of MRD at the level of 10^{-4} to 10^{-5}, with significantly more supporting data from clinical trials. MRD flow is the most widely used method owing to extensive availability and reliable detection at the level of $<10^{-4}$.[40,43] ASO IGH RQ-PCR detects MRD (at the level of $<10^{-5}$), but it is less widely used because it is expensive and more labor-intensive.[44] Consensus recommendations for the methodology for MRD determination, assay requirements and tissue selection (blood vs bone marrow), and the use of MRD in clinical practice versus clinical trials have been published.[45,46]

Several randomized clinical trials showed that uMRD ($<10^{-4}$ detectable leukemic cells in blood or bone marrow) at EoT with venetoclax-based combination regimens with CD20 monoclonal antibody (mAb)[16,17,24,25,36] or ibrutinib[47–49] is an independent predictor of improved survival among patients with newly diagnosed as well as relapsed/refractory CLL. None of these trials studied use of MRD to direct treatment.

In the CLL14 study, at the 3-month follow-up after EoT, the rate of uMRD in the blood was significantly higher with venetoclax + obinutuzumab than with chlorambucil + obinutuzumab (74% vs 34%; $P<.0001$; 40% of patients had uMRD levels of 10^{-6} in the venetoclax + obinutuzumab arm vs 7% in the chlorambucil + obinutuzumab arm), and the uMRD status at EoT also correlated with improved survival outcomes in both treatment arms.[16] The 3-year OS rate for venetoclax + obinutuzumab was 92% for patients with uMRD ($<10^{-4}$) and 73% for those with detectable MRD ($>10^{-2}$).

In the MURANO study, the rate of uMRD at EoT with VenR was 62% compared with 13% after EoT with BR, and the rate of uMRD as best MRD response at any time during the study was also higher with VenR (83% vs 23%).[24] The 5-year follow-up data from the MURANO study also showed that uMRD at EoT with VenR was associated with improved OS.[25] The estimated 3-year survival rate was 95% for patients who had uMRD without disease progression at EoT compared with 85% for those with MRD at EoT. Unmutated IGVH, del(17p), and genomic complexity (≥3 copy number variations) were associated with higher rates of conversion to detectable MRD and subsequent progressive disease after attaining uMRD at EoT. Preexisting mutated *TP53*, *NOTCH1*, and *BIRC3* were associated with lower rates of initial attainment of uMRD among patients treated with VenR.[25,36]

Results from the MRD cohort of the phase II randomized CAPTIVATE study showed that fixed-duration first-line treatment with ibrutinib + venetoclax (ibrutinib lead-in for 3 cycles followed by ibrutinib + venetoclax for 12 cycles; n=164) resulted in high rates of uMRD in both blood (75%) and bone marrow (68%).[47] High uMRD rates were observed in patients across all risk groups, including del(17p)/*TP53* mutation and unmutated IGHV. Among 86 patients with confirmed uMRD randomized to receive either placebo or ibrutinib, the estimated 36-month PFS rates were not significantly different between the 2 treatment arms (95% vs 100%, respectively).[48] Among the 63 patients without confirmed uMRD randomized to receive ibrutinib + venetoclax or ibrutinib, postrandomization uMRD rates were higher with ibrutinib + venetoclax (69% in blood; 66% in bone marrow) than with ibrutinib (48% in blood; 42% in bone marrow).[48] Estimated 36-month PFS rates were 97% for patients in both treatment arms.[48]

In the phase III randomized GLOW study (evaluating fixed-duration ibrutinib + venetoclax vs chlorambucil + obinutuzumab as first-line treatment for CLL in elderly or unfit patients), the uMRD (10^{-4}) rate was significantly higher for ibrutinib + venetoclax in both bone marrow (52% vs 17%; $P<.0001$) and blood (55% vs 39%; $P=.0259$).[49] uMRD (10^{-4}) in bone marrow for ibrutinib + venetoclax was also higher in patients with unmutated *IGHV* (58% vs 44% for those with mutated *IGHV*). The 12-month PFS rate at EoT was >90% for patients in the ibrutinib + venetoclax arm (irrespective of MRD status). In contrast, detectable MRD in blood was associated with earlier relapse in patients treated with chlorambucil + obinutuzumab.

These findings confirm that uMRD status after EoT with venetoclax-based combination regimens is a predictive marker for PFS. MRD assessment may be useful in clinical practice to provide insight into anticipated PFS duration following fixed-duration treatment, but not to reliably recommend treatment duration or in treatment decisions for patients on targeted therapy at the present time.

Management of Adverse Events

BTK Inhibitors

Diarrhea, fatigue, arthralgia, infections, cytopenias, bleeding, and cardiovascular toxicities (including atrial fibrillation, ventricular arrhythmias, and hypertension) are the adverse events (AEs) associated with BTKis (Table 3). Acalabrutinib and zanubrutinib have a more favorable toxicity profile due to the more selective/specific inhibition of BTK. In the ELEVATE-RR head-to-head trial of acalabrutinib versus ibrutinib, treatment discontinuation due to AEs

were lower with acalabrutinib (15% vs 21% for ibrutinib).[27] Atrial fibrillation (9% vs16%), hypertension (9% vs 23%), and bleeding (38% vs 51%) were less frequent with acalabrutinib compared with ibrutinib. Acalabrutinib was associated with a higher rate of headache (35% vs 20% for ibrutinib), with only 2% of patients experiencing grade ≥3 headache. Zanubrutinib was also associated with a substantially lower rate of atrial fibrillation (2.5% vs 10%) compared with ibrutinib in the ALPINE trial, and the rates of major bleeding (3% vs 4%) and treatment discontinuation due to AEs (8% vs 13.0%) were also lower with zanubrutinib.[31] In contrast, neutropenia was more frequent with zanubrutinib (28% vs 22% for ibrutinib); however, this did not translate into a higher rate of infection (60% vs 63% for ibrutinib).

The benefit and risk of BTKis should be evaluated in patients requiring antiplatelet or anticoagulant therapies. Patients requiring warfarin were excluded from clinical trials evaluating acalabrutinib and ibrutinib, whereas the use of anticoagulants including warfarin was not restricted in clinical trials evaluating zanubrutinib. Concomitant administration of ibrutinib or acalabrutinib with warfarin should be avoided. Coadministration of acalabrutinib with proton pump inhibitors should be avoided. Zanubrutinib can be coadministered with anticoagulants, including warfarin and gastric acid–reducing agents (proton pump inhibitors, H2-receptor antagonists).

Hypertension should be managed with antihypertensives as appropriate. Headache is commonly observed with acalabrutinib early in the treatment course and can generally be managed with analgesics (eg, acetaminophen) and caffeine supplements. Monitoring for signs of bleeding, atrial fibrillation, and hypertension along with appropriate management is recommended for patients receiving BTKis.

Switching to alternate therapy can be considered, especially in patients with atrial fibrillation or hypertension that is not medically controllable. Acalabrutinib and zanubrutinib were shown to be effective in the management of patients with ibrutinib intolerance.[50–52]

BCL-2 Inhibitors

Tumor lysis syndrome (TLS) was an important adverse effect of venetoclax in early clinical trials. Initiation at a lower dose (20 mg for 1 week) and gradual step-wise ramp-up over 5 weeks to target dose (400 mg daily) along with TLS prophylaxis are recommended to mitigate the risk and frequency of TLS.[53] Initiation and accelerated dose escalation (20 to 400 mg over 3 weeks) with close inpatient monitoring for TLS can be performed in patients with high tumor burden and for those with rapid disease progression on or following BTKi therapy.[54–56]

Growth factor support should be considered for patients with associated neutropenia. Dose reduction may be necessary for those with persistent neutropenia and limited bone marrow involvement.

Management of Resistance to Small Molecule Inhibitors

Acquired resistance to BTKis is predominantly mediated by *BTK* and *PLCG2* mutations.[57,58] *BTK* and/or *PLCG2* mutations were detected at an estimated median of 9 months before relapse in patients treated with ibrutinib, and these mutations were also detected in patients with progressive CLL during ibrutinib therapy up to 15 months before the manifestation of clinical progression.[57,59] *BTK* C481 mutations were also detected in 69% of patients with disease relapse at an estimated median of 12 months before relapse in patients treated with acalabrutinib.[58] Long-term follow-up is needed to confirm whether *BTK* C481 mutations will emerge in patients treated with zanubrutinib.

Venetoclax is effective for the management of relapsed/refractory CLL after prior treatment with BCRi (ibrutinib or idelalisib),[54,60–62] although the results of a pooled analysis from 4 clinical trials showed that BCRi-refractory CLL was significantly associated with lower CR rate and shorter duration of response.[63] Results from other retrospective analyses suggest that the use of venetoclax is associated with higher ORR and improved PFS following failure of ibrutinib (vs failure of idelalisib) and also in patients who had received only 1 BCRi (vs those who had received >1 BCRi).[64,65]

Acquisition of *BCL-2* mutations (G101V and D103Y) were implicated in resistance to venetoclax.[66,67] *BCL-2* G101V mutation (low variant allele frequency [VAF]) was identified in patients with progressive CLL during venetoclax therapy up to 25 months before clinical progression.[66] Limited available data suggest that subsequent BTKi therapy or retreatment with venetoclax-based regimens is effective in patients with relapsed CLL following treatment with venetoclax whereas PI3Ki following venetoclax do not appear to result in durable remissions.[68–72]

Testing for *BTK* mutations may be helpful to confirm resistance to BTKis. The reported VAFs are variable, with low VAF often associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance.[57,59] Testing for *BTK* or *BCL-2* mutations as screening for resistance to BTKi or venetoclax is not currently recommended. Testing for *BTK* and *PLCG2* mutations may be useful in patients with disease progression or no response while on BTKi therapy. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment.

Summary

Use of targeted therapies as a preferred treatment approach for treatment-naive CLL/SLL significantly transformed the treatment landscape of relapsed/refractory disease. The benefit/risk of continuous versus fixed-duration treatment approach should be carefully evaluated. Optimal sequencing of therapy has yet to be clarified. Careful monitoring of AEs associated with targeted therapies and supportive care for treatment-related complications should be an integral part of CLL/SLL management to achieve the full clinical benefit.

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