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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2024, NCCN Clinical Practice Guidelines in Oncology

Permalink

<https://escholarship.org/uc/item/9bp38306>

Journal

Journal of the National Comprehensive Cancer Network, 22(3)

ISSN

1540-1405

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Publication Date

2024-04-01

DOI

10.6004/jnccn.2024.0018

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Peer reviewed

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma, Version 2.2024

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ABSTRACT

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are essentially different manifestations of the same disease that are similarly managed. A number of molecular and cytogenetic variables with prognostic implications have been identified. Undetectable minimal residual disease at the end of treatment with chemoimmunotherapy or venetoclax-based combination regimens is an independent predictor of improved survival among patients with previously untreated or relapsed/refractory CLL/SLL. The selection of treatment is based on the disease stage, presence or absence of del(17p) or TP53 mutation, immunoglobulin heavy chain variable region mutation status, patient age, performance status, comorbid conditions, and the agent's toxicity profile. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnosis and management of patients with CLL/SLL.

J Natl Compr Canc Netw 2024;22(3):175–204
doi:10.6004/jnccn.2024.0018

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Supplementary material is published online at <https://doi.org/10.6004/jnccn.2024.0018>

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Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Individual disclosures for the NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Panel members can be found on page 204. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

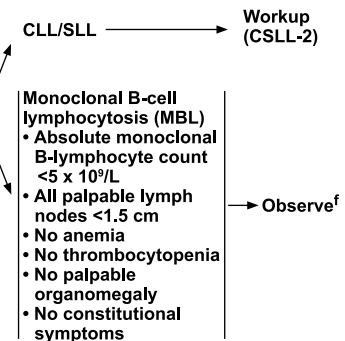
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DIAGNOSIS^a**ESSENTIAL:**

- Hematopathology review of peripheral blood smear and all slides with at least one paraffin block representative of the tumor, if the diagnosis was made on a lymph node or bone marrow biopsy.
- Flow cytometry of blood is adequate for the diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).
 - ▶ CLL diagnosis requires presence of monoclonal B lymphocytes $\geq 5 \times 10^9/L$ in peripheral blood^b
 - ▶ Clonality of B cells should be confirmed by flow cytometry
 - ▶ Adequate immunophenotyping to establish diagnosis by flow cytometry using cell surface markers:^c kappa/lambda, CD19, CD20, CD5, CD23, CD10, CD200; if flow cytometry is used to establish diagnosis, also include cytospin for cyclin D1 or fluorescence in situ hybridization (FISH) for t(11;14); t(11q;v).
 - ▶ SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with monoclonal B lymphocytes $\leq 5 \times 10^9/L$ in peripheral blood
 - ▶ SLL diagnosis should be confirmed by histopathology evaluation of lymph node biopsy
- Biopsy is generally not required. If diagnosis is not established by flow cytometry, then proceed with lymph node biopsy. Bone marrow aspirate with biopsy can be pursued if peripheral blood and lymph node biopsy material are nondiagnostic. Fine-needle aspiration (FNA) or core needle biopsy alone is not generally suitable for the initial diagnosis of CLL/SLL. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core needle biopsy and FNA biopsy in conjunction with appropriate ancillary techniques for the differential diagnosis (ie, immunohistochemistry [IHC], flow cytometry) may be sufficient for diagnosis.
 - ▶ Adequate immunophenotyping to establish diagnosis by IHC:^c CD3, CD5, CD10, CD20, CD23, cyclin D1, LEF1, SOX11^d
- Absolute monoclonal B lymphocyte count^b

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:^e

- FISH to detect: +12; del(11q); del(13q); del(17p)
- TP53 sequencing
- CpG-stimulated metaphase karyotype for complex karyotype (CK)
- Molecular analysis to detect: Immunoglobulin heavy chain variable region gene (IGHV) mutation status
- Beta-2-microglobulin



Footnotes on CSLL-1A

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CSLL-1

Overview

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues.¹ Morphologically, these leukemic cells appear as small, mature lymphocytes that can be found admixed with occasional larger or atypical cells, or prolymphocytes. CLL remains the most prevalent adult leukemia in Western countries. In 2024, an estimated 20,700 people will be diagnosed with CLL in the United States, and an estimated 4,440 people will die of the disease.²

CLL and SLL are essentially different manifestations of the same disease that are similarly managed.¹ 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, while 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.

Staging

The Rai and Binet systems are the 2 staging systems currently used for the evaluation of patients with CLL, both in routine practice and clinical trial settings.^{3,4} Both staging systems rely on physical assessments (ie, presence of lymph

node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to evaluate the degree of tumor burden.

The modified Rai classification stratifies patients into 3 risk groups: low-risk disease (Rai stage 0), intermediate-risk disease (Rai stage I–II), and high-risk disease (Rai stage III–IV) with historic median survival times of 150 months, 71 to 101 months, and 19 months, respectively, in the era of chemotherapy- and chemoimmunotherapy-based treatment.³ Survival times in the current era of targeted therapy will most assuredly be improved and will become available with longer follow-up for patients who received targeted therapies.

The Binet staging system stratifies patients into 3 prognostic groups based on the number of involved areas and the level of hemoglobin and platelets and, like the Rai staging system, provides meaningful correlation with clinical outcome.⁴

The Lugano Modification of the Ann Arbor Staging System is used for patients with SLL.⁵

Prognostic Factors

The prognostic significance of molecular and cytogenetic variables may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated

FOOTNOTES

^a Cases diagnosed as B-cell prolymphocytic leukemia (B-PLL) are excluded from this guideline.

^b Absolute monoclonal B lymphocyte count <5000/mm³ that persists more than 3 months in the absence of palpable adenopathy or other clinical features of lymphoproliferative disorder is MBL. Cells of the same phenotype may be seen in reactive lymph nodes; therefore, diagnosis of SLL should only be made when effacement of lymph node architecture is seen. Bone marrow examination is not helpful for the diagnosis of MBL.

^c Typical immunophenotype: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, slg dim+, and cyclin D1-. Note: Some cases may be slg bright+ or CD23- or dim; some MCL may be CD23+; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases, especially for those with an atypical immunophenotype (ie, CD23 dim or negative, CD20 bright, slg bright). CD200 positivity may distinguish CLL from mantle cell lymphoma (MCL), which is usually CD200-.

^d LEF1 and SOX11 may be helpful in suspected cases of MCL that are cyclin D1-negative.

^e Prognostic Information for CLL/SLL (CSLL-A).

^f Outside of clinical trials, CT scans are not required for diagnosis, serial monitoring, surveillance, routine monitoring of treatment response, or progression.

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CSLL-1A

(See CSLL-A, page 183). The impact of these variables on the clinical outcome are discussed subsequently.

Immunoglobulin Heavy Chain Variable Region Gene Mutation

A cut-off level of 2% or less deviation from germline immunoglobulin heavy chain variable region (IGHV) sequence is routinely used in clinical practice to differentiate patients with IGHV-unmutated CLL from those with IGHV-mutated CLL.⁶⁻⁸ Percent deviation from the germline sequence was studied and higher levels were incrementally associated with favorable progression-free survival (PFS) and overall survival (OS) in patients treated with the FCR regimen (fludarabine, cyclophosphamide, and rituximab), suggesting that IGHV mutation percentage is a continuous variable.⁹

IGHV gene mutation status correlated with time-to-first treatment (TTFT), response rates, PFS, and OS in patients treated with FCR.¹⁰⁻¹² In the CLL10 study, the PFS benefit of FCR was significant in physically fit patients <65 years and in patients with mutated IGHV.¹¹ Among patients with mutated IGHV gene, the median PFS was not reached with FCR compared with 55 months for bendamustine/rituximab (BR; *P* = .089). In a phase II study of 300 patients with previously untreated CLL, IGHV-mutated CLL (>2% mutation or <98% homology with germline gene sequence)

was associated with long-term PFS, with a plateau on the PFS curve beyond 10 years after treatment with FCR (after a median follow-up of 19 years, the median PFS for patients with IGHV-mutated CLL was 15 years vs 4 years for patients with IGHV-unmutated CLL).¹² In a multivariable analysis, IGHV-unmutated status and del(17p) were independently associated with significantly shorter PFS.

Unmutated IGHV (≤2% of mutation or ≥98% homology with germline gene sequence) is associated with unfavorable prognosis and significantly shorter survival compared with mutated IGHV in patients treated with chemoimmunotherapy-based regimens, independent of the stage of the disease.^{13,14} In addition, VH3-21 gene usage is associated with poor outcomes regardless of the IGHV mutation status (as defined by percent homology with germline sequence).¹⁵ Unmutated IGHV and/or the VH3-21 gene usage was shown to be an independent predictor of shorter treatment-free interval and/or survival outcomes in patients treated with fixed-duration chemoimmunotherapy- and venetoclax-based regimens, even when high-risk genetic abnormalities were included in the multivariable regression models.^{16,17} PFS and OS were not correlated with IGHV mutation status in patients treated with continuous Bruton's tyrosine kinase (BTK)-inhibitor (BTKi)-based regimens.¹⁸⁻²⁰

WORKUP**ESSENTIAL:**

- History and physical exam including measurement of size of liver and spleen and palpable lymph nodes
- Performance status
- B symptoms
- Complete blood count (CBC) with differential
- Comprehensive metabolic panel
- Beta-2-microglobulin

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct antiglobulin test (Coombs)
- Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated⁹
- Uric acid
- Lactate dehydrogenase (LDH)
- Unilateral bone marrow aspirate and biopsy (may be informative for the diagnosis of immune-mediated or disease-related cytopenias)
- Hepatitis B^h and C testing if treatment is contemplated
- Pregnancy testing in patients of childbearing age if systemic therapy or RT is planned
- Discussion of fertility preservationⁱ
- FDG-PET/CT scan to direct nodal biopsy, if histologic transformation is suspected.

SLL/Localized
(Lugano Stage I)
(CSLL-3)

CLL (Rai Stages 0–IV)
or
SLL (Lugano Stage II–IV)
(CSLL-3)

⁹ Outside of clinical trials, CT scans are not required for diagnosis, serial monitoring, surveillance, routine monitoring of treatment response, or progression. CT scans may be warranted for the evaluation of symptoms of bulky disease or for the assessment of risk for TLS prior to initiating venetoclax.

^h Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy [CIT], chemotherapy, targeted therapy). See Treatment and Viral Reactivation (CSLL-C 1 of 4)*. Tests include hepatitis B surface antigen (HBsAg) and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with a gastroenterologist.

ⁱ Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

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CSLL-2

Continuous treatment with a covalent BTKi (ibrutinib, acalabrutinib, or zanubrutinib) results in high response rate and survival independent of the IGHV mutation status.^{18,19,21–23} The ELEVATE-TN trial showed that acalabrutinib ± obinutuzumab resulted in greater PFS benefit compared with obinutuzumab + chlorambucil both in IGHV-unmutated and IGHV-mutated CLL; however, in patients with IGHV-mutated CLL, the PFS benefit was significant only for combined acalabrutinib + obinutuzumab.¹⁹ In the ECOG-ACRIN cancer research group (E1912) study, ibrutinib + rituximab resulted in superior PFS compared with FCR in patients with IGHV-unmutated CLL (hazard ratio [HR], 0.27; $P < .001$) and IGHV-mutated CLL (HR, 0.27; $P < .001$).²¹ The biomarker subgroup analysis of the SEQUOIA study confirmed that PFS was significantly better for zanubrutinib (compared with BR) in patients with IGHV-unmutated and IGHV-mutated CLL.²² In the FLAIR study, the PFS was significantly better for ibrutinib + rituximab (compared with FCR) in patients with IGHV-unmutated CLL; however, PFS was not significantly different between the treatment arms among patients with IGHV-mutated CLL.²³

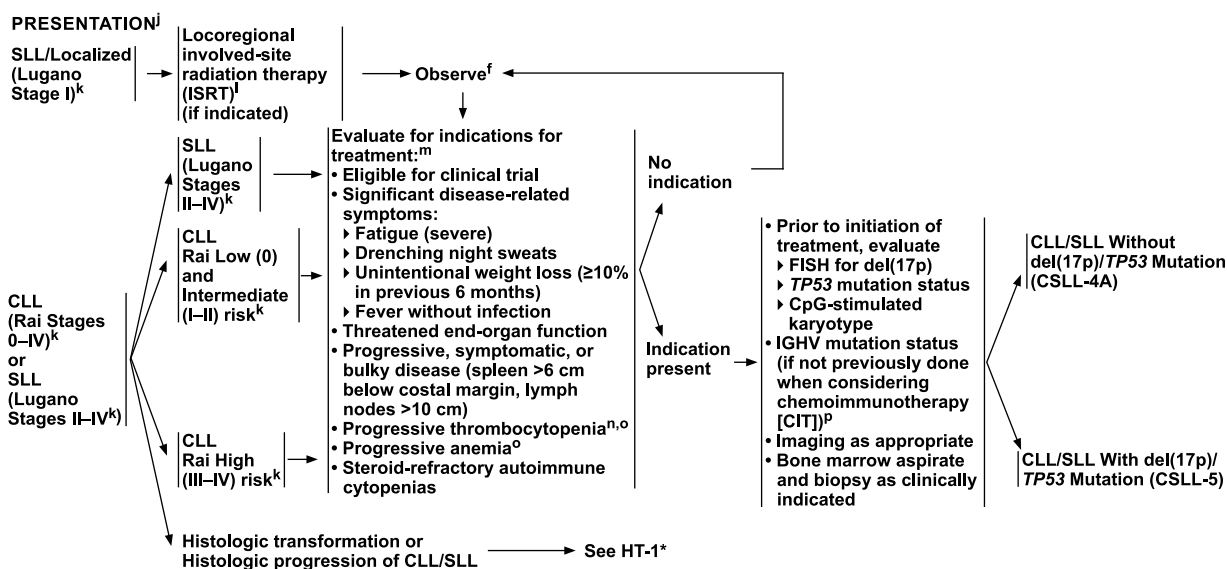
IGHV-unmutated status remains a prognostic factor for shorter PFS after fixed-duration treatment with venetoclax + obinutuzumab (VenO).^{24–27} The extended

follow-up data from the CLL14 study showed that VenO resulted in longer PFS for patients with IGHV-mutated CLL compared with those with IGHV-unmutated CLL (after a median follow-up of 52 months, the median PFS was not reached for patients in the IGHV-mutated group compared with 57 months for those in the IGHV-unmutated group).²⁴ In the phase III randomized GAIA-CLL13 trial, VenO with or without ibrutinib resulted in significant PFS benefit among patients with IGHV-unmutated CLL compared with IGHV-mutated CLL.²⁶ In the multivariable model, IGHV-unmutated status was an independent predictor of shorter PFS in the pooled VenO and VenO + ibrutinib arms.²⁷ Among patients with IGHV-unmutated CLL, the PFS was longer for patients randomized to VenO + ibrutinib compared with VenO.

Cytogenetic Abnormalities

Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) are present in more than 80% of patients with CLL.²⁸

Del(13q) (55%), del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%) are the most common abnormalities at the time of diagnosis. Del(13q) as a sole abnormality was associated with favorable prognosis and the longest median survival (133 months) after



^f Outside of clinical trials, CT scans are not required for diagnosis, serial monitoring, surveillance, routine monitoring of treatment response, or progression.

^j Supportive Care for Patients with CLL/SLL (CSLL-C*).

^k See Rai and Binet Classification Systems (CSLL-B 1 of 2*) and Lugano Modification of Ann Arbor Staging System (CSLL-B 2 of 2*).

^l See NCCN Guidelines for B-Cell Lymphomas, Principles of Radiation Therapy[†] for additional details.

^m Absolute lymphocyte count (ALC) alone is not an indication for treatment in the absence of leukostasis, which is rarely seen in CLL.

ⁿ Platelet counts >100,000/μL are typically not associated with clinical risk.

^o Select patients with mild, stable cytopenia (ANC <1000/μL, Hgb <11 g/dL, or platelet <100,000/μL) may continue to be observed. Other causes of anemia/thrombocytopenia (eg, autoimmune disorders, vitamin/iron deficiency) should be excluded.

^p IGHV mutation status does not change over time and analysis does not need to be repeated if previously done prior to initiation of treatment.

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CSLL-3

chemoimmunotherapy. Del(11q) is often associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 months) after chemoimmunotherapy.

Del(17p) reflects the loss of the *TP53* gene and is frequently associated with mutation in the remaining *TP53* allele. Del(17p) is more frequently observed in patients with previously treated CLL [suggesting that acquisition and/or expansion of CLL clones with del(17p) may occur through treatment]. The prognostic significance of del(17p) may be dependent on the proportion of malignant cells with this abnormality, and the prognosis is more favorable when the percentage of cells with del(17p) is low.^{29,30}

TP53 Aberrations

TP53 aberrations [del(17p) or *TP53* mutation] are predictors of poor outcomes with chemoimmunotherapy. Del(17p) is associated with poor response to chemoimmunotherapy, short treatment-free interval, and inferior survival.^{12,28,31} *TP53* mutations are predictors of poor survival (independent of 17p chromosome status) to chemoimmunotherapy with fludarabine- or bendamustine-based regimens.^{32–36}

TP53 aberrations also remain an independent predictor of inferior PFS and OS for fixed-duration treatment with venetoclax-based regimens.^{25,37} Del(17p) and *TP53* mutation are independent predictors of PFS and OS whereas

del(17p) and/or *TP53* mutation with IGHV-unmutated status is associated with the shortest PFS.^{25,37} Continuous treatment with a covalent BTKi also results in shorter PFS and OS in patients with del(17p) or *TP53*-mutated CLL. The survival outcomes for CLL in patients with *TP53* aberrations treated with either a BTKi-based regimen or a venetoclax-based regimen are much better than the survival outcomes in patients treated with chemoimmunotherapy.

Recurrent Gene Mutations

In addition to *TP53* mutation, recurrent mutations with prognostic implications were identified in *ATM*, *NOTCH1*, *SF3B1*, and *BIRC3* genes. The incidence of these mutations is approximately 4%–15% in patients with newly diagnosed CLL, and the incidences are much higher (15%–25%) in patients with fludarabine-refractory CLL.^{38–42} *ATM*, *SF3B1* and *NOTCH1* mutations were predictors of shorter TTFT independent of IGHV mutation status, whereas *TP53* and *NOTCH1* mutations along with IGHV-unmutated status were predictors of shorter OS.⁴¹ In the CLL14 study, *BIRC3* and *SF3B1* mutations were independent predictors of inferior PFS after chemoimmunotherapy with chlorambucil + obinutuzumab, but these mutations had no impact on the clinical outcome after VenO; however, the follow-up was short.³⁷

CLL/SLL WITHOUT DEL(17p)/TP53 MUTATION^j

FIRST-LINE THERAPY

RESPONSE TO THERAPY^qSECOND-LINE THERAPY^uTHIRD-LINE THERAPY^u

BTK inhibitor (BTKi) ± anti-CD20 mAb (Continuous treatment) See Suggested Regimens (CSLL-D 1 of 6)

or

Venetoclax + obinutuzumab (Fixed duration treatment) See Suggested Regimens (CSLL-D 1 of 6)

CIT or Immunotherapy (CSLL-4B)

Intolerance

Response^q

Progression while on treatment^{q,r,s,t}

Continue treatment with the same BTKi^v until intolerance and/or progression

Observe until relapse with indications for treatment

Progression or intolerance while on treatment^{q,r,t}

Venetoclax ± anti-CD20 mAb or Alternative BTKi

Venetoclax ± anti-CD20 mAb^w or BTKi

BTKi

Alternative BTKi

BTKi

Relapsed or Refractory disease after prior therapy with BTKi^s and venetoclax-based regimens

Clinical trial (preferred) or Consider allogeneic hematopoietic cell transplant (HCT) if without significant comorbidities^x or Other Recommended Regimens (Therapy for Relapsed or Refractory Disease, CSLL-D 2 of 6)

^j Supportive Care for Patients with CLL/SLL (CSLL-C*).

^q Response Definition After Treatment for CLL/SLL (CSLL-E).

^r If progression with indication for subsequent therapy: Re-evaluate with FISH for del(17p)/TP53 mutation status and CpG-stimulated karyotype, prior to initiation of subsequent therapy.

^s Testing for BTK and PLCG2 mutations may be useful in patients with disease progression or no response while on BTKi therapy including if poor adherence is considered as a possible cause. BTK and PLCG2 mutation status alone is not an indication to change treatment in absence of disease progression. Alternative covalent BTKi (acalabrutinib, ibrutinib, or zanubrutinib) could be considered for intolerance in absence of disease progression.

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^t Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation.

^u In patients with disease responding to therapy: Continue the same BTKi until progression and/or intolerance. If treated with venetoclax-based fixed duration treatment, observe until relapse with indications for retreatment. At time of disease progression, transition to next therapy as soon as possible. Treatment-free interval should be as short as possible. It is safe to overlap with venetoclax while on a BTKi.

^v In patients with no intolerance, ibrutinib can be continued until disease progression while following recommended dose modification guidance as needed.

^w Venetoclax + obinutuzumab preferred.

^x ElSawy M, et al. Br J Haematol 2015;170:574-583.

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CSLL-4A

An integrated prognostic model including *NOTCH1*, *SF3B1*, and *BIRC3* mutations along with the cytogenetic abnormalities detected by FISH was proposed to classify patients with newly diagnosed or previously untreated CLL who received rituximab-based chemoimmunotherapy or fludarabine or alkylating agent-based chemotherapy into 4 distinct prognostic subgroups: high-risk (*TP53* and/or *BIRC3* abnormalities); intermediate-risk (*NOTCH1* and/or *SF3B1* mutations and/or del(11q)); low-risk (trisomy 12 and wild-type for all genetic lesions); and very low-risk [del(13q) only].⁴³ The 10-year survival rates for the 4 subgroups were 29%, 37%, 57%, and 69%, respectively. This prognostic model may have limited utility because it excludes the IGHV mutation status.

Complex Karyotype

Complex karyotype (CK; ≥3 unrelated chromosomal abnormalities in >1 cell on CpG-stimulated karyotype of CLL cells) is associated with inferior clinical outcomes. A retrospective analysis of greater than 5,000 patients with available cytogenetic data indicated that CK was associated with variable clinical behavior.⁴⁴ High CK (≥5 unrelated chromosomal abnormalities) emerged as an adverse prognostic factor independent of clinical stage, IGHV mutation status, and *TP53* aberrations [del(17p) and/or *TP53* mutation], whereas

low CK (3 unrelated chromosomal abnormalities) and intermediate CK (4 unrelated chromosomal abnormalities) were clinically relevant only if coexisting with *TP53* aberrations.

CK may be a stronger predictor of poor clinical outcomes than del(17p) or *TP53* mutation in patients with CLL treated with ibrutinib-based regimens.⁴⁵⁻⁴⁸ It should be noted that in these studies, del(17p) often correlated with the presence of CK. Among patients with relapsed/refractory CLL treated with ibrutinib-based regimens, in a multivariable analysis, only CK was significantly associated with shorter event-free survival (EFS; *P* = .006), whereas CK (*P* = .008) and fludarabine-refractory CLL (*P* = .005) were independently associated with shorter OS.⁴⁵ In an analysis of 308 patients treated with ibrutinib on 4 sequential clinical trials, in a multivariable analysis, CK at baseline, presence of del(17p), and age <65 years were all independently associated with shorter time to CLL progression.⁴⁸ In patients ≥65 years without CK or del(17p), the estimated cumulative incidence of CLL progression at 4 years was 2% compared with 44% in patients <65 years with CK and del(17p). CK was not associated with worse PFS in patients with treatment-naïve CLL treated with zanubrutinib in the SEQUOIA study.²²

High CK was an adverse prognostic factor in patients with CLL treated with venetoclax-based combination

CLL/SLL WITHOUT DEL(17p)/TP53 MUTATION^j

FIRST-LINE THERAPY

CIT or Immunotherapy
(Fixed duration treatment)
See Suggested Regimens
based on age and functional
status (CSLL-D 1 of 6)

RESPONSE TO THERAPY^q

Response^q
after
completion
of treatment

Progression or
intolerance while
on treatment^{q,r,t}

Observe until
relapse with
indications
for
treatment

SECOND-LINE THERAPY^u

Suggested Regimens (CSLL-D 2 of 6)

Venetoclax ± anti-
CD20 mAb

or

BTKi

BTKi

→

Venetoclax ±
anti-CD20 mAb

→

Relapsed or
refractory disease
after prior therapy
with BTKi-^s and
venetoclax-based
regimens

→

Clinical trial (preferred)
or
Consider allogeneic
HCT if without
significant
comorbidities^x
or
Other Recommended
Regimens^y (Therapy for
Relapsed or Refractory
Disease, CSLL-D 2 of 6)

^j Supportive Care for Patients with CLL/SLL (CSLL-C*).

^q Response Definition After Treatment for CLL/SLL (CSLL-E).

^r If progression with indication for subsequent therapy: Re-evaluate with FISH for del(17p)/TP53 mutation status and CpG-stimulated karyotype, prior to initiation of subsequent therapy.

^s Testing for *BTK* and *PLCG2* mutations may be useful in patients with disease progression or no response while on BTKi therapy including if poor adherence is considered as a possible cause. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment in absence of disease progression. Alternative covalent BTKi (acalabrutinib, ibrutinib, or zanubrutinib) could be considered for intolerance in absence of disease progression.

^t Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation.

^u In patients with disease responding to therapy: Continue the same BTKi until progression and/or intolerance. If treated with venetoclax-based fixed duration treatment, observe until relapse with indications for retreatment. At time of disease progression, transition to next therapy as soon as possible. Treatment-free interval should be as short as possible. It is safe to overlap with venetoclax while on a BTKi.

^x ElSawy M, et al. *Br J Haematol* 2015;170:574-583.

^y CIT or immunotherapy is not an option for patients who have received these regimens for first-line therapy.

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CSLL-4B

regimens.⁴⁹ In a prospective analysis of the GAIA-CLL13 trial, CK (≥ 3 unrelated chromosomal abnormalities) was associated with shorter PFS (HR, 2.6; $P < .001$) and OS (HR, 3.25; $P = .044$) among patients treated with chemoimmunotherapy, whereas only high CK (≥ 5 unrelated chromosomal abnormalities) was an independent adverse prognosticator for PFS in the pooled venetoclax arms.⁴⁹ Chemoimmunotherapy resulted in the acquisition of additional chromosomal abnormalities whereas CK remained stable after treatment with venetoclax-based regimens.

Beta-2 Microglobulin

Beta-2 microglobulin is readily measured by standard laboratory evaluation of blood samples, and an elevated level of serum beta-2 microglobulin was shown to be a strong independent prognostic indicator for treatment-free interval, response to treatment, and OS in patients treated with first-line chemoimmunotherapy.^{50,51} Beta-2 microglobulin was incorporated in prognostic models for the risk stratification of patients with CLL.⁵²⁻⁵⁵ However, it is influenced in a CLL disease-independent manner by renal dysfunction.

Prognostic Models

Several scoring systems and prognostic models incorporating traditional and newer prognostic markers were

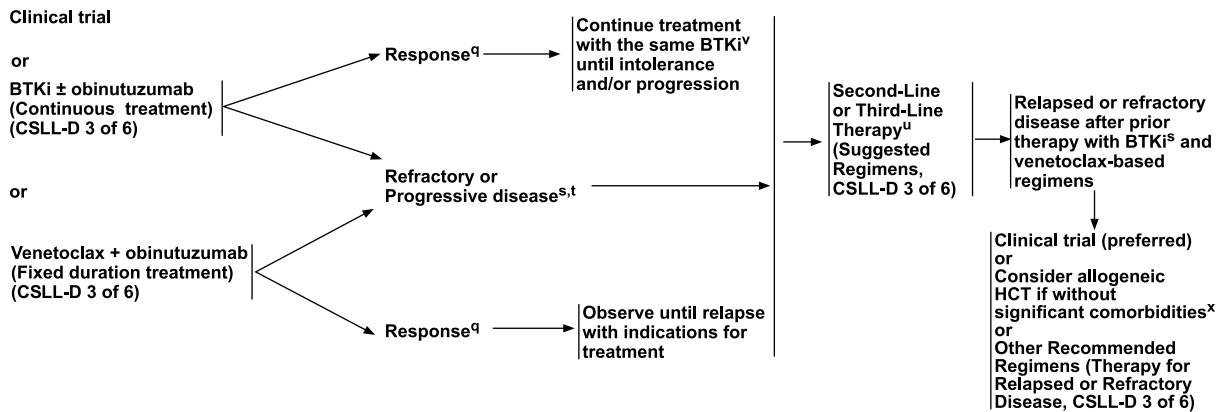
developed to more accurately predict the clinical course of disease and outcomes to treatment in patients with CLL/SLL.

A prognostic nomogram and a more simplified prognostic index (based on age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes) is useful in estimating TTFT in patients with untreated CLL, including those with early-stage disease, and the utility of this prognostic index was confirmed in several studies.^{53,56,57} The simplified prognostic index is also useful in estimating survival probability and stratifies patients with untreated CLL into 3 different risk groups (low, intermediate, and high) with different survival outcomes.⁵³ The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.

In another prognostic model, increased size of cervical lymph nodes, 3 involved nodal sites, del(17p) or del(11q), unmutated IGHV status, and elevated serum lactate dehydrogenase levels were identified as independent predictors of shorter TTFT.⁵⁸ This model may help to identify patients with newly diagnosed CLL at high risk for disease progression who may be candidates for clinical trials of interventions to delay TTFT with chemoimmunotherapy.

CLL/SLL WITH DEL(17p)/TP53 MUTATION^jFIRST-LINE THERAPY^zRESPONSE
TO THERAPY^q

ADDITIONAL THERAPY

^j Supportive Care for Patients with CLL/SLL (CSLL-C*).^q Response Definition After Treatment for CLL/SLL (CSLL-E).^s Testing for *BTK* and *PLCG2* mutations may be useful in patients with disease progression or no response while on BTKi therapy including if poor adherence is considered as a possible cause. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment in absence of disease progression. Alternative covalent BTKi (acalabrutinib, ibrutinib, or zanubrutinib) could be considered for intolerance in absence of disease progression.^t Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation.^u In patients with disease responding to therapy: Continue the same BTKi until progression and/or intolerance. If treated with venetoclax-based fixed duration treatment, observe until relapse with indications for retreatment. At time of disease progression, transition to next therapy as soon as possible. Treatment-free interval should be as short as possible. It is safe to overlap with venetoclax while on a BTKi.^v In patients with no intolerance, ibrutinib can be continued until disease progression while following recommended dose modification guidance as needed.^x ElSawy M, et al. *Br J Haematol* 2015;170:574-583.

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CSLL-5

The Integrated CLL Scoring System (ICSS) is based on the cytogenetic abnormalities detected by FISH, IGHV mutation status, and CD38 expression.⁵⁹ ICSS stratified patients into 3 risk groups (low, intermediate, and high) with different TTFT and OS. ICSS is also helpful to identify patients with a high likelihood of early progression who would be candidates for clinical trials evaluating early interventions.

The International Prognostic Index for CLL (CLL-IPI) is based on *TP53* and IGHV mutation status, serum beta-2 microglobulin concentration, clinical stage, and age.⁵² The CLL-IPI was validated in an independent cohort of patients with newly diagnosed CLL and is useful for predicting TTFT and risk of progression in patients receiving first-line chemoimmunotherapy.⁶⁰ CLL-IPI stratifies patients into 4 risk groups (low, intermediate, high, and very high) with significantly different OS. The 5-year OS rates were 93%, 79%, 63%, and 23%, respectively for the 4 risk groups.

The International Prognostic Score for Early-Stage CLL (IPS-E) predicts the likelihood of disease progression to need treatment in patients with early-stage CLL and stratifies patients with early-stage CLL into 3 risk groups with significantly different TTFT.⁶¹ The cumulative risk for the need of treatment after 1 and 5 years of observation was 14% and 61%, respectively, for patients with

high-risk IPS-E compared with 2% and 28% for patients with intermediate-risk IPS-E and <0.1% and 8% for patients with low-risk IPS-E. These findings need to be validated in a prospective clinical trial.

Targeted therapies with small molecule inhibitors have significantly improved survival outcomes and prognostic models were developed to predict the outcome of patients treated with targeted therapies.^{54,55} The first prognostic model is predictive of survival in patients treated with ibrutinib and stratified patients into 3 risk groups (high [3–4 points]; intermediate [2 points]; and low [0 points]) based on *TP53* aberrations, prior treatment, elevated serum beta-2 microglobulin and lactate dehydrogenase.⁵⁴ The 3-year PFS rates were 47%, 74%, and 87% for the high-, intermediate-, and low-risk groups, respectively ($P < .0001$). The corresponding 3-year OS rates were 63%, 83%, and 93%, respectively ($P < .0001$). This model remained significant in the stratification of patients with treatment-naïve and relapsed/refractory CLL. The second prognostic model identified patients with high-risk previously treated CLL who do not achieve a good outcome with available targeted therapies (ibrutinib, idelalisib, and venetoclax).⁵⁵ This prognostic model stratified patients into 3 risk groups based on elevated serum beta-2 microglobulin and lactate dehydrogenase,

PROGNOSTIC INFORMATION FOR CLL/SLL^a

Method of Detection	Prognostic Variable	Risk Category
Interphase cytogenetics (FISH) ^b	del(17p)	Unfavorable
	del(11q)	Unfavorable
	+12	Intermediate
	Normal	Intermediate
	del(13q) (as a sole abnormality)	Favorable
DNA sequencing ^c	TP53	Wild-type: Favorable Mutated: Unfavorable
	IGHV	>2% mutation: Favorable ≤2% mutation: Unfavorable
CpG-stimulated metaphase karyotype	CK ^d (≥3 unrelated clonal chromosome abnormalities in more than one cell on karyotype)	Unfavorable

^a This table provides useful prognostic information for survival and time to progression in patients who received CIT-based treatment. The significance of these prognostic variables in patients treated with targeted therapy are less well-defined.
^b Formal studies identifying the percentage of abnormal cells identified by FISH are ongoing, although populations less than 10% appear to not have the clinical impact as noted in the table. The presence of del(11q) and/or del(17p) are associated with short progression-free survival (PFS) with chemotherapy and CIT approaches.
^c IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated. TP53 mutation status also provides additional prognostic information to FISH.
^d CK is based on results of metaphase karyotyping of CpG-stimulated CLL cells.

hemoglobin, and time from initiation of last therapy (<24 months): low (score 0–1); intermediate (score 2–3); and high risk (score 4).

Response Criteria

The response criteria developed by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) are outlined in the algorithm on CSLL-E (page 188). In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. The iwCLL guidelines provide further recommendations for the evaluations and response assessments appropriate for the general clinical practice setting versus for clinical trials.⁶²

Treatment with both covalent BTKi (ibrutinib, acalabrutinib, zanubrutinib) and noncovalent BTKi (pirtobrutinib) and phosphatidylinositol 3-kinase inhibitors (PI3Ki; idelalisib and duvelisib) cause mobilization of lymphocytes into blood early during treatment initiation, resulting in a transient lymphocytosis in most patients, which does not signify disease progression. Prolonged lymphocytosis following ibrutinib treatment was reported to represent the persistence of a quiescent clone, and slow or incomplete resolution of lymphocytosis does not appear to impact outcome as measured by PFS.⁶³

Considering these findings, the iwCLL response criteria were revised to more precisely predict the outcome of patients with CLL treated with BTKi and PI3Ki.⁶⁴ The revised iwCLL response criteria allow for the response category, partial response (PR) with lymphocytosis (PR-L). In patients receiving BTKi (ibrutinib, acalabrutinib, zanubrutinib, or pirtobrutinib) or PI3Ki (idelalisib or duvelisib), this response category includes clinical response (reduction in lymph nodes and splenomegaly with persistent lymphocytosis, in the absence of other indicators of progressive disease). Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

Minimal Residual Disease

Assessment of measurable residual disease (MRD; also referred to as *minimal residual disease*) is a highly sensitive indicator of disease burden in patients with CLL and MRD assessment because part of response evaluation is incorporated into some clinical trials. 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 were published.^{65,66}

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	Useful in Certain Circumstances
• Acalabrutinib^{f,g,*} ± obinutuzumab (category 1) • Venetoclax^{f,h} + obinutuzumab (category 1) • Zanubrutinib^{f,g,*} (category 1)	• Ibrutinib^{f,g,i,*} (category 1) • Ibrutinib^{f,g,*} + obinutuzumab (category 2B) • Ibrutinib^{f,g,*} + rituximab^j (category 2B) • Ibrutinib^{f,g,*} + venetoclax^{f,h} (category 2B)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▶ FCR (fludarabine, cyclophosphamide, rituximab)^{k,l,m} • Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed ▶ Bendamustineⁿ + anti-CD20 mAb^{o,p} ▶ Obinutuzumab ± chlorambucil^q ▶ High-dose methylprednisolone (HDMP) + anti-CD20 mAb^o (category 2B; category 3 for patients <65 y without significant comorbidities)

* Covalent (irreversible) BTKi.

Footnotes on CSLL-D 4 of 6**Suggested Regimens for Second-Line and Third-Line Therapy for CLL/SLL without del(17p)/TP53 Mutation (CSLL-D 2 of 6)****Therapy for Relapsed or Refractory Disease After Prior BTKi-and Venetoclax-Based Regimens for CLL/SLL Without del(17p)/TP53 Mutation (CSLL-D 2 of 6)****Suggested Regimens for CLL/SLL With del(17p) (CSLL-D 3 of 6)**

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CSLL-D
1 OF 6

MRD detection can be performed by several methods with different sensitivities using either blood or bone marrow. A commercial next-generation sequencing (NGS)-based assay was reported to be more sensitive allowing for the detection of MRD at the level of 10^{-6} (MRD6) and is the only assay currently available in the United States that is cleared by the FDA.^{67–70} NGS-based assays require collection of a pretreatment sample. Multicolor (≥ 4) flow cytometry and allele-specific oligonucleotide IGHV real-time quantitative polymerase chain reaction (ASO-PCR) are the 2 other methods used for the detection of MRD at the level of 10^{-4} (MRD4) to 10^{-5} (MRD5) with significantly more supporting data from clinical trials. MRD flow is the most widely used method owing to the extensive availability and reliable detection at the level of $<10^{-4}$.⁷¹ ASO-PCR detects MRD at the level of $<10^{-5}$; however, it is less widely used since it is expensive and more labor intensive.⁷²

BTKi monotherapy does not typically result in undetectable MRD (uMRD) but the use of covalent BTKi in combination with anti-CD20 monoclonal antibody (mAb) results in higher rates of uMRD compared with monotherapy.^{19,35,73} In the E1912 phase III randomized trial that compared FCR versus ibrutinib + rituximab, among patients randomized to ibrutinib + rituximab there was

no significant difference in PFS rates based on uMRD status.⁷⁴ PFS was significantly longer in patients with MRD levels of 10^{-1} and continuous treatment with ibrutinib was necessary to maintain treatment efficacy. The prognostic value of uMRD has not been confirmed in the context of BTKi monotherapy or in combination with anti-CD20 mAb.

uMRD4 at the end of treatment (EOT) with chemoimmunotherapy or venetoclax-based combination regimens is an independent predictor of improved survival among patients with previously untreated as well as relapsed/refractory CLL. Several randomized clinical trials showed that venetoclax-based combination regimens result in higher rates of undetectable MRD (uMRD; $<10^{-4}$, uMRD4 or $<10^{-6}$, uMRD6 in blood or bone marrow) than chemoimmunotherapy. uMRD4 rates at the EOT with venetoclax-based combination regimens from selected trials are summarized in Table S1 in the Supplementary material (available online with this article).

The association between uMRD status at EOT and PFS are discussed subsequently. However, it should be noted that none of the trials studied the use of MRD to direct treatment. MRD assessment may be useful in clinical practice to provide insight into anticipated PFS duration, but not to reliably recommend treatment duration

SUGGESTED TREATMENT REGIMENS^{a,b,c,d}
CLL/SLL Without del(17p)/TP53 Mutation

SECOND-LINE OR THIRD-LINE THERAPY ^e		
Preferred Regimens • Acalabrutinib^{f,g,r,*} (category 1) • Venetoclax^{f,h} + rituximab (category 1) • Zanubrutinib^{f,g,r,*} (category 1)	Other Recommended Regimens • Ibrutinib^{f,g,i,*} (category 1) • Venetoclax^{f,h} • Ibrutinib^{f,g,*} + venetoclax^{f,h} (category 2B)	Useful in Certain Circumstances • For relapse after a period of remission (if previously used) ▶ Venetoclax^{f,h} ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) • Resistance or intolerance to prior covalent BTKi therapy ▶ Pirtobrutinib^{i,**}

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi- AND VENETOCLAX-BASED REGIMENS ^e
Other Recommended Regimens (alphabetical order by category) • Small-molecule inhibitors^f ▶ Duvelisib ▶ Idelalisib^g ± rituximab ▶ Pirtobrutinib^{i,**} (if not previously given) ▶ Ibrutinib^{g,*} + venetoclax^h (category 2B) • FCR^{j,l,m} • Lenalidomide^t ± rituximab • Obinutuzumab • Bendamustineⁿ + rituximab^p (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb^p (category 2B)

* Covalent (irreversible) BTKi.

** Non-covalent (reversible) BTKi.

Footnotes on CSLL-D 4 of 6

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

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CSLL-D
2 OF 6

or treatment decisions for patients on targeted therapy at the present time. At the present time, MRD assessment is not recommended (outside of clinical trials) as part of response evaluation.

Previously Untreated CLL/SLL

Chemoimmunotherapy

In the combined analysis of 2 randomized phase III studies (CLL8 and CLL10), MRD status at the EOT with chemoimmunotherapy correlated with better survival in a multivariable analysis.⁷⁵ Among patients who experienced complete response (CR) and PR, PFS was longer for those with uMRD4 CR and uMRD4 PR (61 and 54 months, respectively) than those with MRD-positive CR and MRD-positive PR (35 and 21 months, respectively).⁷⁵ The persistence of posttreatment splenomegaly as a sole abnormality in patients with uMRD4 did not have a negative impact on PFS.

In a prospective study of 289 patients with previously untreated CLL, uMRD4 at the EOT with FCR correlated with longer PFS.⁷⁶ The median PFS was not reached for patients with uMRD compared with 38 months for those with detectable MRD ($P < .001$). MRD level ($\leq 1\%$ vs $> 1\%$) after 3 courses of FCR predicted greater likelihood of achieving uMRD by the EOT (64% vs 9%; $P < .001$). PFS

was significantly longer for patients with MRD $\leq 1\%$ versus $> 1\%$ after 3 courses of FCR (median 73 vs 41 months, $P < .001$), but similar for $< 0.01\%$ versus 0.01%–1%.

Venetoclax + Obinutuzumab (With or Without Ibrutinib)

In the CLL14 study, uMRD4 status at the EOT correlated with improved survival in both treatment arms.²⁵ Deeper uMRD remissions (uMRD5 and uMRD6) were more frequent with VenO and PFS was longer in patients with uMRD6 compared with those with detectable MRD4 at EOT. The 4-year PFS rates were 77% for patients with uMRD6 and 36% for those with detectable MRD4. The 4-year OS rate was 89% for patients with uMRD4 and 64% for those with detectable MRD4.

In the phase III randomized GAIA–CLL13 trial, VenO (with or without ibrutinib) resulted in significantly higher uMRD4 rates ($P < .001$) compared with chemoimmunotherapy, but the uMRD4 rate was not significantly higher with venetoclax + rituximab (VenR; $P = .32$).²⁶ At 15 months after EOT, more patients experienced uMRD6 with VenO (60%) and VenO + ibrutinib (66%) than with chemoimmunotherapy (23%).²⁷ After a median follow-up of 51 months, uMRD6 was associated with longer PFS compared with detectable MRD6 in patients randomized to VenO with or without ibrutinib.²⁷

SUGGESTED TREATMENT REGIMENS^{a,b,c,d}

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

(alphabetical by category)

CIT is not recommended since del(17p)/TP53 mutation is associated with low response rates.

FIRST-LINE THERAPY ^e		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
- Acalabrutinib^{f,g,*} ± obinutuzumab - Venetoclax^{f,h} + obinutuzumab - Zanubrutinib^{f,g,*}	- Ibrutinib^{f,g,i,*} - Ibrutinib^{f,g,*} + venetoclax^{f,h} (category 2B)	- Consider when BTKi and venetoclax are not available or contraindicated or rapid disease debulking needed - HDMP + anti-CD20 mAb^o - Obinutuzumab
SECOND-LINE OR THIRD-LINE THERAPY ^e		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
- Acalabrutinib^{f,g,r,*} (category 1) - Venetoclax^{f,h} + rituximab (category 1) - Venetoclax^{f,h} - Zanubrutinib^{f,g,r,*} (category 1)	- Ibrutinib^{f,g,i,*} (category 1) - Ibrutinib^{f,g,*} + venetoclax^{f,h} (category 2B)	- For relapse after a period of remission (if previously used) - Venetoclax^{f,h} ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) - Resistance or intolerance to prior covalent BTKi therapy - Pirtobrutinib^{f,**}
THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi- AND VENETOCLAX-BASED REGIMENS ^e		
Other Recommended Regimens - Small-molecule inhibitors^f (in alphabetical order by category) - Duvelisib - Idelalisib^o ± rituximab - Pirtobrutinib^{**} (if not previously given) - Ibrutinib^{g,*} + venetoclax^h (category 2B) - Alentuzumab^u ± rituximab - HDMP + anti-CD20 mAb^o - Lenalidomide^t ± rituximab		

* Covalent (Irreversible) BTKi.

** Non-covalent (reversible) BTKi.

Footnotes on CSLL-D 4 of 6

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

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CSLL-D
3 OF 6**Ibrutinib + Venetoclax**

The results of the phase II randomized CAPTIVATE study showed that fixed-duration treatment with ibrutinib + venetoclax resulted in high rates of uMRD4 in all subgroups [del(17p) and/or mutated TP53, del(11q), and IGHV-unmutated CLL]. In the fixed-duration cohort, uMRD4 rates were 81% (blood) and 41% (bone marrow) for patients with del(17p) and/or mutated TP53; uMRD4 rates were higher in patients with IGHV-unmutated CLL (84% in blood; 64% in bone marrow) compared with IGHV-mutated CLL (67% in blood; 53% in bone marrow).⁷⁷ In the MRD cohort, patients were assigned to subsequent treatment based on the uMRD4 status at EOT.^{78,79} Patients without confirmed uMRD4 were randomized to receive ibrutinib + venetoclax (n=32) or ibrutinib (n=31); postrandomization uMRD4 rates were higher with ibrutinib + venetoclax than with ibrutinib.⁷⁸ The estimated 3-year PFS rates were 97% for patients in both treatment arms. Patients with confirmed uMRD4 (n=86) were randomized to receive placebo or ibrutinib. The estimated 4-year PFS rates were 95% for those assigned to ibrutinib and 88% for those assigned to placebo. The 4-year OS rates were not significantly different for the 2 treatment arms (100% and 98%, respectively).⁷⁹

In the phase III randomized GLOW study, a higher rate of uMRD4 at 3 months after EOT (EOT+3) was observed

with fixed-duration ibrutinib + venetoclax across all subgroups, including del(11q) and IGHV-unmutated CLL.^{80,81} The estimated PFS rate for patients with uMRD4 in the bone marrow at 12 months after EOT (EOT+12) was 96% for ibrutinib + venetoclax compared with 83% for chlorambucil + obinutuzumab.⁸¹ The rate of uMRD5 was also higher with ibrutinib + venetoclax (45% in blood; 40% in bone marrow) compared with chlorambucil + obinutuzumab (22% in blood and 6% in bone marrow). After a median follow-up of 55 months, PFS benefit was observed, particularly in patients with IGHV-unmutated CLL, who experienced uMRD4 at EOT+3; PFS rates at 3 years after EOT were also higher with ibrutinib + venetoclax among patients with IGHV-mutated CLL independent of the MRD status at EOT+3.⁸²

Treatment with ibrutinib + venetoclax for 2 years resulted in high uMRD4 rates in patients with previously untreated CLL/SLL.^{83,84} In the interim analysis of the FLAIR study (274 patients randomized between ibrutinib and ibrutinib + venetoclax), the uMRD4 response rates were higher in patients with IGHV-unmutated CLL (83% in blood; 80% in bone marrow) compared with IGHV-mutated CLL (64% in blood; 56% in bone marrow) within 2 years of treatment with ibrutinib + venetoclax.⁸³ Large ongoing clinical trials will help to clarify the optimal duration of first-line treatment with combined targeted

SUGGESTED TREATMENT REGIMENS
FOOTNOTES

- ^a See references for regimens on CSLL-D 5 of 6* and CSLL-D 6 of 6*.
- ^b 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 mAb 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 mAbs poses the same risk of recurrence.
- ^e An FDA-approved biosimilar is an appropriate substitute for rituximab.
- ^f Please refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.
- ^g A baseline cardiovascular risk assessment should be considered prior to initiation of covalent BTKi.
- ^h Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-F).
- ⁱ The panel consensus to list ibrutinib under "other recommended regimens" is based on the toxicity profile.
- ^j Recommended only for patients aged <65 y without significant comorbidities.
- ^k Data from the CLL10 study confirmed 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).
- ^l See Discussion for further information on oral fludarabine.
- ^m 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.
- ⁿ For patients aged ≥65 y or patients aged <65 y with significant comorbidities (CrCl <70 mL/min) dose is 70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated.
- ^o Anti-CD20 mAbs include: rituximab or obinutuzumab.
- ^p Not recommended for frail patients.
- ^q Recommended only for patients aged ≥65 y or patients aged <65 y with significant comorbidities (creatinine clearance [CrCl] <70 mL/min).
- ^r 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.
- ^s 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).
- ^t 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.
- ^u 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*).

*Available online, in these guidelines, at NCCN.org.

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therapy and the importance of the difference in uMRD rates between IGHV-mutated and IGHV-unmutated CLL with different regimens.

Relapsed/Refractory CLL/SLL

In the MURANO study comparing VenR vs BR, uMRD as best MRD response at any time during the study was higher with VenR (83% vs 23%) and the 5-year follow-up data showed that uMRD at the EOT with VenR was associated with improved PFS and OS.^{85,86} The 3-year PFS rates after EOT were 61% for those with uMRD4 compared with 41% for those with low-MRD-positive disease (10^{-4} to $<10^{-2}$). The 3-year OS rates after EOT were 95% and 73%, respectively, for those with uMRD4 and low-MRD-positive disease (10^{-4} to $<10^{-2}$) or high-MRD-positive disease ($>10^{-2}$).⁸⁶ Unmutated IGHV, del(17p), and genomic complexity (≥ 3 copy number variations) were associated with higher rates of conversion to detectable MRD4 and subsequent progressive disease after attaining uMRD4 at EOT.⁸⁶ Pre-existing *TP53*, *NOTCH1*, and *BIRC3* mutations were associated with lower rates of initial attainment of uMRD4 among patients treated with VenR.⁸⁷

The results of the phase II single-arm CLARITY study showed that treatment with ibrutinib + venetoclax also resulted in high rates of uMRD4 in patients with relapsed/refractory CLL/SLL.^{88,89} The duration of treatment was

based on the time to achieve uMRD4 in both blood and bone marrow (14 months for patients with uMRD4 at 8 months; 26 months for those with uMRD4 at 14 months and/or at 26-month follow-up; venetoclax was discontinued and ibrutinib was given until disease progression in patients with detectable MRD at 26 months). In an exploratory analysis, the achievement of uMRD4 after 6 months or a 2-log reduction in MRD levels after 2 months of treatment with ibrutinib + venetoclax resulted in sustained uMRD4 status and ability to discontinue treatment.⁸⁹

These findings confirm that uMRD4 after EOT with venetoclax-based combination regimens is an independent predictor of longer PFS.

Diagnosis

The diagnosis of CLL requires the presence of at least 5×10^9 /L monoclonal B-lymphocytes in the peripheral blood and the clonality of B cells should be confirmed by flow cytometry (CSLL-1).⁶² The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with less than 5×10^9 /L monoclonal B lymphocytes in the peripheral blood.⁶² B cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when there is effacement of the lymph node architecture by histology.

RESPONSE DEFINITIONS AFTER TREATMENT FOR CLL/SLL^a

Parameter	CR	PR	PD ^b	SD
Group A				
Lymph nodes	None ≥ 1.5 cm in longest dimension	Decrease $\geq 50\%$ from baseline ^c	Increase $\geq 50\%$ from baseline or from response	Change of -49% to $+49\%$
Liver and/or spleen size ^d	Spleen size < 13 cm; liver size normal	Decrease $\geq 50\%$ from baseline	Increase $\geq 50\%$ from baseline or from response	Change of -49% to $+49\%$
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	Normal	Decrease $\geq 50\%$ from baseline	Increase $\geq 50\%$ over baseline ^b	Change of -49% to $+49\%$
Group B				
Platelet count	$\geq 100,000/\mu\text{L}$	$\geq 100,000/\mu\text{L}$ or increase $\geq 50\%$ over baseline	Decrease $\geq 50\%$ over baseline secondary to CLL	Change of -49% to $+49\%$
Hemoglobin	≥ 11 g/dL (untransfused and without erythropoietin)	≥ 11 g/dL or increase $\geq 50\%$ over baseline	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or $< 50\%$ over baseline, or decrease < 2 g/dL
Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by $\geq 50\%$ on successive biopsies	No change in marrow infiltrate
Neutrophils without growth factors	$\geq 1500/\mu\text{L}$			

Group A criteria define the tumor load. Group B criteria define the function of the hematopoietic system (or marrow).

Complete remission (CR): All of the criteria have to be met.

Partial remission (PR): At least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve.

Progressive disease (PD): At least 1 of the criteria of group A or group B has to be met.

Stable disease (SD): All of the criteria have to be met; constitutional symptoms alone do not define PD.

Minimal Residual Disease (MRD) Assessment (CSLL-E 2 of 2)

Footnotes on CSLL-E 2 of 2

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Immunophenotype by flow cytometry (blood) is adequate for the diagnosis of CLL; bone marrow biopsy is generally not required. A diagnosis of SLL should ideally be confirmed by lymph node biopsy. Evaluation of cyclin D1 (flow cytometry or IHC) or FISH analysis for t(11;14), flow cytometry evaluation of CD200, IHC for LEF1 and SOX11 may be helpful in the differential diagnosis of CLL, especially be helpful in suspected cases of mantle cell lymphoma that are cyclin D1-negative.^{90–93}

FISH for the detection of del(11q), del(13q), trisomy 12, del(17p), CpG-stimulated metaphase karyotype, *TP53* sequencing, and molecular genetic analysis for IGHV mutation status can provide useful prognostic information and may guide selection of therapy.

Interphase FISH is the standard method to detect specific chromosomal abnormalities that may have prognostic significance. Conventional metaphase karyotype is difficult in CLL due to the very low in vitro proliferative activity of the leukemic cells. CpG oligonucleotide stimulation can be used to enhance metaphase cytogenetics.^{94,95}

Molecular analysis for IGHV mutation status is preferred over flow cytometry. IGHV mutation testing is recommended based on reproducibility and ready availability. IGHV mutation status is necessary when considering treatment with chemoimmunotherapy.

Monoclonal B-Cell Lymphocytosis

Monoclonal B-cell lymphocytosis (MBL) is a condition in which an abnormal monoclonal B-cell population with the immunophenotype of CLL is present but does not meet the diagnostic criteria for CLL (see CSLL-1, page 176).^{96,97} An absolute monoclonal B-lymphocyte count of $< 5 \times 10^9/\text{L}$ that is stable over a 3-month period in the absence of palpable lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder (ie, anemia, thrombocytopenia, constitutional symptoms, organomegaly) is defined as MBL.⁹⁸

MBL is further categorized into low-count MBL ($< 0.5 \times 10^9/\text{L}$) that rarely progresses to CLL and high-count MBL ($0.5\text{--}4.9 \times 10^9/\text{L}$) that can progress to CLL requiring therapy at a rate of 1%–2% per year.^{99,100} High-count MBL is distinguished from Rai 0 CLL based on whether the monoclonal B-cell count is above or below $5 \times 10^9/\text{L}$.¹⁰¹ A nodal variant characterized by nodal infiltration of CLL-line cells without apparent proliferation centers and absence of lymphadenopathy was also described in a subset of patients with MBL.¹⁰²

MBL is associated with favorable molecular characteristics, including mutated IGHV and del(13q), lower prevalence of del(11q)/del(17p) and wild-type *TP53*, slower lymphocyte doubling time, longer treatment-free survival,

RESPONSE DEFINITIONS AFTER TREATMENT FOR CLL/SLL^a**Minimal Residual Disease (MRD) Assessment:**

- Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of fixed duration treatment is an important predictor of efficacy.^{e,f,g,h,i}
- 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} .^{j,k} 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} .^{l,m,n}
- 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.

^a Hallek M, Cheson B, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood* 2018;131:2745-2760.

^b Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

^c Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

^d Spleen size is considered normal if <13 cm. There is no firmly established international consensus on the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

^e Al-Sawaf O, Zhang C, Jin HY, et al. Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. *Nat Commun* 2023;14:2147.

^f Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: Primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE Study. *J Clin Oncol* 2021;39:3853-3865.

^g Munir T, Moreno C, Owen C, et al. Impact of minimal residual disease on progression-free survival outcomes after fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in the GLOW study. *J Clin Oncol* 2023;41:3689-3699.

^h Seymour JF, Kipps TJ, Eichhorst BF, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab. *Blood* 2022;140:839-850.

ⁱ Thompson PA, Peterson CB, Strati P, et al. Serial minimal residual disease (MRD) monitoring during first-line FCR treatment for CLL may direct individualized therapeutic strategies. *Leukemia* 2018;32:2388-2398.

^j Rawstron AC, Kreuzer KA, Soosapilla A, et al. Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. *Cytometry B Clin Cytom* 2018;94:121-128.

^k Wierda WG, Rawstron AC, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. *Leukemia* 2021;35:3059-3072.

^l Rawstron AC, Fazi C, Agathangelidis A, et al. A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study. *Leukemia* 2016;30:929-936.

^m Logan AC, Gao H, Wang C, et al. High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment. *Proc Natl Acad Sci U S A* 2011;108:21194-21199.

ⁿ Aw A, Kim HT, Fernandes SM, et al. Minimal residual disease detected by immunoglobulin sequencing predicts CLL relapse more effectively than flow cytometry. *Leuk Lymphoma* 2018;59:1986-1989.

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CSLL-E
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and very low rate of progression to CLL.⁹⁷ Observation is recommended for all individuals with MBL.

Workup

The workup for CLL/SLL is outlined in CSLL-2 (page 178). Quantitative immunoglobulin levels may be informative in patients with recurrent infections. Measurement of beta-2 microglobulin may provide useful prognostic information.⁵³ Reticulocyte count and a direct Coombs test should be performed to evaluate for the possibility of hemolysis and pure red cell aplasia in patients with anemia.

Bone marrow involvement (diffuse vs nodular) is no longer a prognostic factor with the availability of more reliable prognostic markers that can be analyzed using peripheral blood (eg, IGHV mutation status and cytogenetic abnormalities detected by FISH). Thus, bone marrow biopsy ± aspirate is no longer considered essential for the diagnostic or prognostic evaluation of patients with suspected CLL, but it may be informative to confirm the presence of immune-mediated or disease-related cytopenias before the start of treatment.

CT scans are not generally recommended for routine monitoring of treatment response or disease progression in asymptomatic patients. CT scans may be useful for the evaluation of symptoms of bulky disease, or for the

assessment of risk for tumor lysis syndrome (TLS) before the start of venetoclax and for treatment response assessment in patients with SLL. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.^{103,104}

Assessment of Functional Status and Comorbidity

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).¹⁰⁵ 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.¹⁰⁶

Cumulative Illness Rating Scale (CIRS), Charlson Comorbidity Index, and the NCI Comorbidity Index are some of the scoring systems that can be used to assess comorbidities in patients with CLL. CIRS in combination with creatinine clearance (CrCl) was used by the GCLLSG to assess the overall fitness of patients enrolled in clinical trials.^{106,107} In the CLL14 study, CIRS score >6 or an estimated CrCl <70 mL/min was used as the eligibility criteria for patients with significant comorbidities.^{108,109}

VENETOCLAX: RECOMMENDED TLS PROPHYLAXIS AND MONITORING BASED ON TUMOR BURDEN^a

- Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule.
- For patients with CrCl <80 mL/min and medium tumor burden, consider management as high risk for TLS.

Tumor Burden ^b	Prophylaxis ^c	Blood Chemistry Monitoring ^{e,f}
Low All lymph nodes <5 cm AND Absolute lymphocyte count (ALC) <25 x 10 ⁹ /L	• Oral hydration (1.5–2 L) • Allopurinol^d	Outpatient • Pre-dose, 6–8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium Any lymph node 5 cm to <10 cm OR ALC ≥25 x 10 ⁹ /L	• Oral hydration (1.5–2 L) and consider additional intravenous hydration • Allopurinol	Outpatient • Pre-dose, 6–8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for patients with CrCl <80 mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High Any lymph node ≥10 cm OR ALC ≥25 x 10 ⁹ /L AND any lymph node ≥5 cm	• Oral hydration (1.5–2 L) and intravenous hydration (150–200 mL/h as tolerated) • Allopurinol or febuxostat • Consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Pre-dose, 4, 8, 12, and 24 hours Outpatient at subsequent ramp-up doses • Pre-dose, 6–8 hours, 24 hours

^a Prescribing information for venetoclax. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208573s027b1.pdf.

^b Lymph node size should be evaluated by chest/abdominal/pelvic CT scan with contrast.

^c Administer intravenous hydration for any patient who cannot tolerate oral hydration.

^d Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

^e Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

^f For patients at risk of TLS, monitor blood chemistries at 6–8 hours and at 24 hours at each subsequent ramp-up dose.

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CSLL-F

First-Line Therapy

Localized SLL (Lugano stage I)

Locoregional radiation therapy (RT) is an appropriate induction therapy for patients with symptomatic localized disease (CSLL-3). In rare patients, RT may be contraindicated or may be a suboptimal therapy due to the presence of comorbidities or the potential for long-term toxicity. Patients with localized SLL that progressed after initial RT should be treated as described in the subsequent section for patients with SLL (Lugano stage II–IV).

SLL (Lugano Stage II–IV) or CLL (Rai Stages 0–IV)

Early-stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. In a randomized prospective phase III study of patients with early-stage high-risk CLL, although FCR resulted in high overall response rate (ORR) (93%) and significantly prolonged EFS (median not reached vs 19 months; $P < .001$) compared with watch and wait, there was no significant OS benefit (5-year OS rate was 83% with FCR compared with 80% for watch and wait).¹¹⁰ The results of the CLL12 trial did not demonstrate survival benefit for early treatment with ibrutinib in patients with early-stage, high-risk CLL (high-risk defined according to the GCLLSG index).¹¹¹

These results confirm that a “watch and wait” approach remains the appropriate management strategy for all patients, in the absence of disease symptoms. Treatment will be beneficial if patients become symptomatic or show evidence of progressive disease.⁶² Selected patients with mild, stable cytopenia may continue to be observed and other causes of anemia or thrombocytopenia should be excluded.

Indications for initiating treatment include severe fatigue, weight loss, night sweats, and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); progressive anemia or thrombocytopenia; or steroid-refractory autoimmune cytopenia (CSLL-3).⁶² Absolute lymphocyte count alone is not an indication for treatment in the absence of leukostasis, which is rarely seen in patients with CLL.

In patients with indications for initiating treatment, age, functional status, comorbidities, and the presence or absence of del(17p) or *TP53* mutation should help to direct treatment options as outlined in CSLL-4A, CSLL-4B and CSLL-5 (pages 180, 181, and 182). Re-evaluation for *TP53* mutation status and del(17p) by FISH, and IGHV mutation status (if not previously done) are recommended before starting treatment. IGHV mutation status is important for the selection of initial treatment when considering chemoimmunotherapy and is helpful in

discussing the anticipated remission duration with fixed-duration targeted therapy. CpG-stimulated karyotyping is useful to identify patients with high-risk CLL, particularly for treatment with targeted agents and developing a long-term treatment strategy.

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. Covalent BTKis (acalabrutinib, ibrutinib, and zanubrutinib) are given continuously until disease progression, whereas venetoclax-based combination regimens offer a fixed-duration treatment with a treatment-free remission period. As discussed previously, fixed-duration treatment with venetoclax-based combination regimens also results in higher rates of uMRD, which is an independent predictor of improved survival.

The NCCN CLL Panel stratified all the regimens into 3 categories (based on the evidence, efficacy, toxicity, pre-existing comorbidities, and in some cases access to certain agents): preferred regimens, other recommended regimens, and useful in certain circumstances.

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

Preferred Regimens

Covalent BTKi (acalabrutinib ± obinutuzumab, zanubrutinib) and VenO are included as preferred treatment options, based on the results of the phase III randomized studies (ELEVATE-TN, SEQUOIA, and CLL14).^{19,20,109}

The efficacy data are discussed subsequently and are summarized in Supplementary Table 2.

Acalabrutinib ± Obinutuzumab

In the phase III ELEVATE-TN trial, acalabrutinib ± obinutuzumab resulted in superior PFS compared with chlorambucil + obinutuzumab in patients with previously untreated CLL.¹⁹ Acalabrutinib + obinutuzumab was associated with a PFS benefit in patients with IGHV-unmutated CLL as well as IGHV-mutated CLL compared with chlorambucil + obinutuzumab. At a median follow-up of 75 months, 72-month PFS rate was longer with acalabrutinib + obinutuzumab compared with acalabrutinib (78% vs 62%). There was also a trend toward improved OS for acalabrutinib + obinutuzumab (72-month OS rate was 84% compared with 76% for acalabrutinib monotherapy), although the study was not powered to compare the PFS benefit between the 2 acalabrutinib arms.¹¹²

Acalabrutinib was granted broad FDA approval for the treatment of patients with untreated and relapsed/refractory CLL based on the results of the ELEVATE-TN and ELEVATE-RR trials.^{19,113} Acalabrutinib ± obinutuzumab is included with a category 1 recommendation for all patients with CLL without del(17p) or TP53 mutation (see CSLL-D, 1 of 6, page 184).

Venetoclax + Obinutuzumab

The CLL14 study established VenO as an effective fixed-duration chemotherapy-free first-line treatment option with significantly improved PFS compared with chlorambucil + obinutuzumab in patients ≥65 years or younger patients with comorbidities (CIRS score >6 or an estimated CrCl <70 mL/min).^{108,109} The uMRD4 rate at the EOT was significantly higher with VenO (74% vs 34%; $P<.0001$), and this combination was also associated with lower rate of conversion to MRD-positive status 1 year after treatment.²⁴

VenO was granted broad FDA approval for the treatment of patients with CLL and is included with a category 1 recommendation for patients ≥65 years or younger patients with significant comorbidities (see CSLL-D, 1 of 6, page 184).

The efficacy of VenO in patients <65 years of age without significant comorbidities was established in the phase III randomized GAIA-CLL13 trial.²⁶ The 4-year follow-up data confirmed that VenO with or without ibrutinib was associated with superior PFS compared with chemoimmunotherapy (FCR or BR).²⁷ The panel members agreed that VenO is also an appropriate fixed-duration chemotherapy-free treatment option for younger patients without comorbidities and the panel consensus was to include VenO with a category 1 recommendation for patients <65 years of age without significant comorbidities (CSLL-D, 1 of 6, page 184).

Zanubrutinib

Zanubrutinib is a highly selective/specific covalent BTKi that is FDA-approved for the treatment of CLL. In the phase III SEQUOIA study, zanubrutinib resulted in higher ORR and statistically significant improvement in PFS compared with BR in patients with untreated CLL without del(17p)/TP53 mutation (HR, 0.42; $P<.0001$).²⁰ The biomarker subgroup analysis from the SEQUOIA study confirmed that PFS benefit with zanubrutinib was observed in all subgroups including patients with del(11q) ($P<.001$), unmutated IGHV ($P<.0001$) and mutated IGHV ($P<.01$).²²

Based on the results of the SEQUOIA study, zanubrutinib is included with a category 1 recommendation (see CSLL-D, 1 of 6, page 184).

Other Recommended Regimens

Ibrutinib

In the RESONATE-2 study, after a median follow-up of 5 years, ibrutinib resulted in a significantly higher ORR ($P<.0001$) and significantly longer PFS rate ($P<.0001$) compared with chlorambucil in patients ≥65 years without del(17p).¹¹⁴ With 57% of patients switching to ibrutinib after disease progression on chlorambucil, the estimated 5-year

OS rate was also higher with ibrutinib (without censoring for crossover from chlorambucil). Ibrutinib also improved PFS compared with chlorambucil in patients with high-risk CLL and the estimated 5-year PFS rates were 79% and 67%, respectively, for patients with del(11q) and unmutated IGHV. Extended long-term data confirmed the sustained PFS benefit of ibrutinib as first-line therapy for patients with CLL, including those with high-risk genomic features of unmutated IGHV (HR, 0.109) or del(11q) (HR, 0.033).¹⁸

The Alliance North American Intergroup Study (A041202) showed primary benefit for ibrutinib and ibrutinib + rituximab in patients with unmutated IGHV (61% of patients had unmutated IGHV) rather than mutated IGHV.^{35,36} The presence of CK did not have an impact on PFS among patients treated with ibrutinib. The estimated 2-year PFS rates were 91% and 87%, respectively, for ibrutinib and ibrutinib + rituximab among patients with CK.

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 as first-line therapy only in patients ≥ 65 years without del(17p).^{18,114} The ECOG-ACRIN cancer research group (E1912) study and the FLAIR study (median age: 62 years; patients > 75 years and $> 20\%$ del(17p) cells were excluded) showed that ibrutinib + rituximab was more effective than FCR for patients ≤ 70 years without del(17p)/TP53 mutation, especially for those with unmutated IGHV, indicating that ibrutinib may also be an appropriate option for younger patients with IGHV unmutated CLL.^{21,23,115}

Ibrutinib is included with a category 1 recommendation for patients ≥ 65 years or younger patients with significant comorbidities as well as for patients < 65 years without del(17p) or TP53 mutation (CSLL-D, 1 of 6, page 184). The panel consensus to list ibrutinib under other recommended regimens is based on the toxicity profile. Randomized clinical trials demonstrated a more favorable toxicity profile for acalabrutinib and zanubrutinib (compared with ibrutinib).^{113,116}

Ibrutinib + Obinutuzumab or Rituximab

Ibrutinib + obinutuzumab was approved by the FDA for first-line therapy based on the results of the iLLUMINATE study and there are no randomized clinical trials that compare ibrutinib versus ibrutinib + obinutuzumab.⁷³

The E1912 and FLAIR studies showed that ibrutinib + rituximab was more effective than FCR for patients ≤ 70 years without del(17p)/TP53 mutation, especially for those with unmutated IGHV, indicating that ibrutinib may also be an appropriate option for younger patients with IGHV unmutated CLL.^{21,23} The results of 2 other randomized phase III trials confirmed that ibrutinib + rituximab is more effective than chemoimmunotherapy for previously untreated CLL without del(17p) or TP53 mutation in patients ≥ 65 years or younger patients with comorbidities.^{35,36,73,117}

However, the addition of rituximab to ibrutinib did not result in improved clinical outcomes compared with ibrutinib monotherapy in these 2 randomized studies. In the Alliance North American Intergroup Study (A041202), the estimated 48-month PFS rates were 76% for both ibrutinib + rituximab and ibrutinib monotherapy.³⁶ In a single-center randomized study of 208 patients with high-risk CLL (27 patients with untreated CLL), at a median follow-up of 36 months, the estimated PFS rates were 86% and 87%, respectively, for ibrutinib and ibrutinib + rituximab.¹¹⁷

In all of the previously mentioned randomized clinical trials that evaluated ibrutinib + rituximab or obinutuzumab, ibrutinib was given continuously until disease progression or intolerance and obinutuzumab or rituximab was added to the combination arm only for the first 6 cycles. Therefore, the consensus was that the longer PFS was more the result of continuous and indefinite treatment with ibrutinib, rather than due to the contribution of an anti-CD20 mAb (rituximab or obinutuzumab) during the first 6 months of treatment. Improved outcomes with addition of an anti-CD20 mAb may more likely be seen with fixed-duration treatment with this regimen.

Ibrutinib + rituximab (for patients < 65 years without significant comorbidities) and ibrutinib + obinutuzumab are included with a category 2B recommendation (see CSLL-D, 1 of 6, page 184).

Ibrutinib + Venetoclax

The results of the CAPTIVATE study showed that fixed-duration treatment with ibrutinib + venetoclax results in improved PFS with high rates of durable response and uMRD4 across all patient subgroups.⁷⁷⁻⁷⁹ In the fixed-duration cohort, with a median follow-up of 28 months, the estimated 24-month PFS rate was 95% for the overall study population [96% for patients without del(17p)/TP53 mutation; 93% and 97%, respectively, for those with unmutated IGHV and mutated IGHV].⁷⁷ The estimated 24-month OS rates were 98% for the overall study population and also for patients without del(17p).

PFS was also significantly longer for ibrutinib + venetoclax compared with chlorambucil + obinutuzumab in the GLOW trial.^{80,81} The 55-month follow-up data showed that ibrutinib + venetoclax was also associated with improved OS compared with chlorambucil + obinutuzumab.⁸² The FLAIR study demonstrated that ibrutinib + venetoclax is also superior to FCR in terms of PFS in patients without del(17p)/TP53 mutation.⁸⁴

In the GLOW trial, ibrutinib + venetoclax was associated with significant toxicity (grade ≥ 3 adverse events occurred in 76% of patients and atrial fibrillation [any grade] was reported in 14% of patients) and treatment-related deaths were reported in 7% of patients.⁸⁰ Cardiac or sudden deaths during treatment occurred in patients with a CIRS score of ≥ 10 or an Eastern Cooperative

Oncology Group performance-status score (ECOG PS) of 2 and 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.

The combination of ibrutinib + venetoclax is not FDA approved for the treatment of CLL/SLL in the United States. Based on the safety profile and the absence of data from randomized studies comparing this combination with other approved targeted therapies, the panel consensus was to include ibrutinib + venetoclax as a category 2B recommendation under other recommended regimens (see CSLL-D, 1 of 6, page 184).

Useful in Certain Circumstances

Chemoimmunotherapy

With multiple randomized trials showing the superior efficacy of covalent BTKi- and venetoclax-based combination regimens over chemoimmunotherapy, the panel acknowledges that chemoimmunotherapy should no longer be the preferred first-line treatment option for the vast majority of patients. However, most panel members acknowledge that chemoimmunotherapy (discussed subsequently) may be an acceptable treatment option in selected circumstances: fit patients with IGHV-mutated CLL, in instances when rapid disease debulking is needed or in a small fraction of patients in whom BTKi and venetoclax-based regimens are contraindicated (CSLL-D, 1 of 6, page 184).

Fludarabine, Cyclophosphamide, and Rituximab

The FCR regimen results in high response rates and improved PFS and OS in specific subgroups of fit patients with previously untreated CLL, especially in those with mutated IGHV.^{10,12,21,118}

FCR could be considered as a first-line therapy option for IGHV-mutated CLL in patients <65 years without significant comorbidities because the FCR regimen results in high response rates and improved PFS and OS in this specific subgroup of patients with previously untreated CLL, with a plateau on the PFS curve beyond 10 years.^{10,12,118}

Bendamustine + Anti-CD20 Monoclonal Antibody

In the CLL10 study, although the PFS benefit of FCR was significant in physically fit patients <65 years, there was no significant difference in PFS between BR and FCR as first-line therapy for CLL without del(17p) in patients >65 years.¹¹⁸ The incidence of severe neutropenia and infections was significantly more frequent in the FCR arm, especially among patients >65 years, and the incidences of secondary acute myeloid leukemia or myelodysplastic syndrome were also significantly higher in the FCR arm.¹¹⁸

Bendamustine + anti-CD20 mAb (rituximab or obinutuzumab) may be a reasonable alternative for patients

≥65 years or younger patients with significant comorbidities.^{118–120}

Obinutuzumab ± Chlorambucil

Given the favorable tolerability profile, obinutuzumab monotherapy or in combination with chlorambucil might be an acceptable treatment option for a small fraction of patients for whom more intensive regimens are not appropriate.^{121–123}

Obinutuzumab ± chlorambucil is included with a category 2A recommendation for patients ≥65 years or younger patients with significant comorbidities (CrCl <70 mL/min).

High-Dose Methylprednisolone + Rituximab or Obinutuzumab

High-dose methylprednisolone (HDMP) + rituximab was associated with a lower risk of myelosuppression and lower incidences of infectious complications (attributed to treatment in the frontline setting, good performance status of the patients, use of anti-infective prophylaxis during treatment, and the administration of intravenous immunoglobulin to patients with infections and hypogammaglobulinemia).^{124,125}

HDMP + rituximab or obinutuzumab is included with a category 2B recommendation for patients ≥65 years or younger patients with significant comorbidities and a category 3 recommendation for patients <65 years without significant comorbidities.

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

Limited data are available from prospective clinical studies on the efficacy of covalent BTKis or BCL2 inhibitors as first-line therapy for patients with del(17p)/TP53 mutated CLL. Patients with del(17p) CLL were not eligible for enrollment in the RESONATE-2 study, the E1912 study, the GLOW study, the FLAIR study, and the GAIA-CLL13 study.^{18,21,23,26,80} Chemoimmunotherapy is contraindicated for del(17p)/TP53 mutated CLL due to low response rates.

In the RESONATE-2 study, the OS benefit with ibrutinib was observed in patients with TP53 mutation, del(11q), and/or unmutated IGHV, and the estimated 5-year PFS rate was 56% for the group of 12 patients with TP53 mutation.¹⁸ 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 34 treatment-naïve patients with TP53 aberrations [32 patients with del(17p); 2 patients with TP53 mutation without del(17p); median age 62 years], ibrutinib resulted in an ORR of 97% (30% CR; 64% PR; 3% PR-L) and the estimated 6-year PFS and OS were 61% and 79%, respectively.¹²⁶

Results from the pooled analysis of clinical trials (PCYC-1122e, E1912, RESONATE-2, and iLLUMINATE)

also confirmed the long-term safety and efficacy of ibrutinib as first-line therapy in patients with *TP53* aberrations.¹²⁷ With a median follow-up of 50 months, the estimated 4-year PFS and OS rates were 79% and 88%, respectively. The ORR was 93% (CR in 39% of patients). As mentioned previously, the RESONATE-2 study, and the E1912 study excluded patients with del(17p) CLL and *TP53* mutation was identified retrospectively. Additionally, there are also data suggesting that *TP53* mutation in the absence of del(17p) also confers increased risk. However, it may not be as notable as that associated with the concurrent presence of *TP53* mutation and del(17p).³³

In the CAPTIVATE study (n=159; 27 patients had del(17p) and/or *TP53* mutation), the estimated 24-month PFS and OS rates for ibrutinib + venetoclax were 84% and 96%, respectively, for those with del(17p)/*TP53* mutation.⁷⁷

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.¹⁹ In patients with del(17p) and/or *TP53* mutation, the estimated 72-month PFS rate was 56% for both acalabrutinib + obinutuzumab and acalabrutinib monotherapy, indicating no benefit with the addition of obinutuzumab to acalabrutinib. The estimated 72-month OS rates were 68%, 72%, and 53% for acalabrutinib, acalabrutinib + obinutuzumab, and chemoimmunotherapy, respectively.¹¹²

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.²⁰ In the prospectively enrolled nonrandomized cohort [111 patients with del(17p)/*TP53* mutated CLL], single-agent zanubrutinib resulted in a higher ORR and statistically significant improvement in PFS compared with BR. The best ORR and 18-month PFS rates were 98% and 89%, respectively, for patients with high del(17p) (≥20%), and 92% and 88%, respectively, for patients with low del(17p) (>7% to <20%).¹²⁸

In the CLL14 study, the PFS benefit for VenO was also seen across all patient subgroups including those with del(17p) or *TP53* mutation [del(17p) or mutated *TP53* were seen in only 8% and 12% of patients, respectively].¹⁰⁹

Enrollment in an appropriate clinical trial is recommended for patients with untreated del(17p) CLL. Given currently available data (as discussed previously), acalabrutinib ± anubrutinib, anubrutinib, and VenO are included as preferred treatment options for first-line therapy with a category 2A recommendation (see CSLL-D, 3 of 6, page 186).^{19,20,109}

Ibrutinib (category 1) and ibrutinib + venetoclax (category 2B) are included as options under other recommended regimens (CSLL-D, 3 of 6, page 186). The panel consensus to list ibrutinib under other recommended regimens is based on the toxicity profile.

The panel emphasizes that the efficacy of BTKi-based regimens in del(17p) CLL/SLL exceeds that of the other regimens and BTKi-based regimens should be considered as the best choice in the absence of a contraindication to covalent BTKi. HDMP + rituximab or obinutuzumab^{124,125} or obinutuzumab¹²¹ can be considered in selected circumstances when rapid disease debulking is needed or in a small fraction of patients in whom covalent BTKi and venetoclax-based regimens are contraindicated (see CSLL-D, 3 of 6, page 186).

Second-Line and Subsequent Therapy

In patients with disease responding to covalent BTKi, treatment should be continued until progression and/or intolerance. If treated with fixed-duration venetoclax-based treatment or chemoimmunotherapy, observation is recommended until relapse with indications for retreatment.

In patients with relapsed/refractory disease requiring treatment, the selection of second-line therapy should be based on the type of first-line therapy, duration of remission, and acquired resistance to treatment. Recommendations for the selection of second-line therapy based on outcomes after first-line therapy are outlined on CSLL-4A, CSLL-4B, and CSLL-5 (pages 180, 181, and 182).

The efficacy data from randomized clinical trials that evaluated small-molecule inhibitors for relapsed/refractory CLL/SLL are discussed subsequently and are summarized in Supplementary Table S3.

BTK Inhibitors

Covalent BTK Inhibitors

Acalabrutinib, ibrutinib, and zanubrutinib are also approved for treatment of relapsed/refractory CLL/SLL based on the results of phase III randomized studies (ASCEND, ELEVATE-RR, RESONATE, and ALPINE trials).^{113,116,129,130} 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 47 months, the median PFS was 46 months and the 42-month PFS rate was 62% for patients with del(17p)/*TP53* mutation assigned to acalabrutinib.¹²⁹ 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) or del(11q) CLL.¹¹³

The final analysis of the RESONATE study showed that the presence of del(17p)/*TP53* mutation or CK was not associated with inferior PFS outcomes to ibrutinib.¹³⁰ In an exploratory analysis that combined data from patients with del(17p) and *TP53* mutation, the median PFS was 41 months for patients 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 or refractory del(17p) CLL (n=145), demonstrating an ORR of 83% (as assessed by the independent review committee).¹³¹

The randomized phase III study (ALPINE) showed that zanubrutinib resulted in a significantly higher ORR and significantly longer PFS in patients with relapsed/refractory CLL/SLL.¹¹⁶ Zanubrutinib also resulted in a higher ORR and longer PFS across the major subgroups of patients, including those with a del(17p) and/or *TP53* mutation. Among patients with del(17p) and/or *TP53* mutation, the 36-month PFS rate was 60% for zanubrutinib and 44% for ibrutinib. The 3-year follow-up data also confirmed the superior efficacy and tolerability of zanubrutinib over ibrutinib.¹³²

Covalent BTKi (acalabrutinib, ibrutinib, or zanubrutinib) are recommended options for second-line and subsequent therapy with a category 1 recommendation, irrespective of the del(17p)/*TP53* mutation status (CSLL-D, 2 of 6, page 185; CSLL-D 3 of 6, page 186). Acalabrutinib and zanubrutinib are listed as options for preferred regimens. Ibrutinib is included as an option under other recommended regimens based on the toxicity profile.

Non-Covalent BTK Inhibitor

Pirtobrutinib was approved for the treatment of patients with relapsed/refractory CLL/SLL who received at least 2 prior lines of therapy, including a BTKi and BCL-2 inhibitor, based on the results from the BRUIN study.^{133,134}

In this phase I-II study, among the patients previously treated with a BTKi (n=247), pirtobrutinib resulted in an ORR of 73% (82% including PR-L) and the median PFS was 20 months.¹³³ At a median follow-up of 23 months, the estimated 18-month OS rate was 81% for patients previously treated with a BTKi. In the subgroup of patients previously treated with the BTKi and venetoclax-based regimen (n=100), the ORR was 70% (79% including PR-L) and the median PFS was 17 months.¹³³ The estimated median PFS was 17 months and 19 months, respectively, for patients with del(17p) or *TP53* mutation and those with unmutated IGHV.

The ORR (including PR-L) was higher irrespective of the status of prior therapy with BCL-2 inhibitors (83% for BCL-2 inhibitor naïve and 80% for BCL-2 inhibitor exposed); however, PFS was longer in the BCL-2 inhibitor-naïve group than in the BCL-2 inhibitor-exposed group (23 and 16 months, respectively).¹³⁴ The 24-month OS rates were 83% and 61%, respectively.

Pirtobrutinib is included as an option [useful in certain circumstances; irrespective of del(17p)/*TP53* mutation] for patients with intolerance to prior covalent BTKi therapy or

for those with disease that is resistant to covalent BTKi (CSLL-D, 2 of 6, page 185; CSLL-D 3 of 6, page 186).^{133,134} It is also an option [if not previously used; irrespective of del(17p)/*TP53* mutation] for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens.

BCL-2 Inhibitor

VenR is approved for the treatment of relapsed/refractory CLL/SLL based on the results of the phase III randomized MURANO trial.^{86,135} 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 also higher for VenR (62% vs 13% for BR).⁸⁶

Venetoclax monotherapy resulted in an ORR of 77% (63% in patients who received prior therapy with a BTKi (ibrutinib) or PI3Ki (idelalisib) in patients with relapsed or refractory del(17p) CLL.¹³⁶ 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 BTKi or PI3Ki).

Venetoclax is also effective for relapsed/refractory CLL after prior treatment with ibrutinib or idelalisib,¹³⁷⁻¹⁴⁰ although the results of a pooled analysis from four clinical trials showed that CLL refractory of BTKi or PI3Ki was significantly associated with lower CR rate and shorter duration of response.¹⁴¹ Results from other retrospective analyses suggest that the use of venetoclax is associated with higher ORR and improved PFS following disease progression on ibrutinib (compared with disease progression on idelalisib) and also in patients who had received only one BTKi or PI3Ki (compared with those who had received >1 BTKi or PI3Ki).^{142,143}

An international retrospective study showed that retreatment with the venetoclax-based regimen (Ven2) is feasible and effective for patients with CLL previously treated with a venetoclax-based regimen (Ven1) in any line of therapy.¹⁴⁴ Among 46 patients with CLL retreated with the venetoclax-based regimen (response data were available for 39 patients; a median of 16 months between the completion of Ven1 and initiation of Ven2), Ven2 resulted in an ORR of 80% (33% CR). At a median follow-up of 10 months, the median PFS was 25 months.

VenR is included as a preferred treatment option for second-line and subsequent therapy with a category 1 recommendation, irrespective of the del(17p)/*TP53* mutation status (CSLL-D, 2 of 6, page 185; CSLL-D 3 of 6, page 186). Venetoclax monotherapy is an option with a category 2A recommendation (a preferred regimen for CLL with del(17p)/*TP53* mutation; CSLL-D 3 of 6).

Retreatment with venetoclax ± anti CD20 mAb (VenO is preferred) is an option for disease relapse after a period of remission (if previously used as first-line

therapy), irrespective of del(17p)/*TP53* mutation (CSLL-D, 2 of 6; CSLL-D 3 of 6).¹⁴⁵

Ibrutinib + Venetoclax

The results of the phase II CLARITY study (n=53) showed that treatment with combined ibrutinib and venetoclax was effective for relapsed/refractory CLL resulting in an ORR of 89% (51% CR), and this combination also resulted in higher rates of uMRD4.⁸⁸ This study included patients with relapsed/refractory CLL/SLL after prior chemoimmunotherapy or idelalisib and patients treated with prior BTKi or venetoclax were excluded.

The panel consensus was to include ibrutinib + venetoclax as an option [other recommended regimens; irrespective of del(17p)/*TP53* mutation] with a category 2B recommendation based on the results of the CLARITY study (CSLL-D, 2 of 6; CSLL-D 3 of 6; pages 185 and 186).⁸⁸ This combination is also an option (category 2B) for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens [if not previously used; irrespective of 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 relapsed/refractory CLL/SLL.^{146–151}

In a phase III randomized trial (220 patients; CIRS >6, decreased renal function, or cumulative marrow toxicity from prior therapy; randomized to receive IdR or rituximab + placebo), IdR demonstrated efficacy in patients relapsed/refractory CLL/SLL with and without del(17p). IdR significantly prolonged survival in patients with del(17p) or *TP53* mutation compared with those treated with rituximab + placebo but there was no difference in survival benefit compared with those without del(17p).¹⁴⁷ The median OS was 29 months for patients treated with IdR compared with 15 months for those treated with rituximab + placebo. IdR is FDA approved for relapsed/refractory CLL based on the results of this study and is available for clinical use with a black box warning regarding the risks of fatal and serious toxicities including hepatotoxicity, diarrhea, colitis, pneumonitis, and intestinal perforation.

Idelalisib monotherapy also demonstrated activity in relapsed/refractory SLL.¹⁴⁸ The indication for idelalisib monotherapy in relapsed/refractory SLL was withdrawn by the manufacturer as 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.¹⁴⁸

Duvelisib also significantly extended median PFS (17 vs 9 months) compared with ofatumumab in the subgroup

of patients with del(17p).¹⁴⁹ In the DUO crossover extension study (that evaluated the efficacy and safety of duvelisib monotherapy in patients with disease progression while receiving ofatumumab in the DUO trial), the ORR was 77% (61% PR) for the subset of 26 patients with del(17p) and/or *TP53* mutations.¹⁵¹

Duvelisib and idelalisib ± rituximab are included as options for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens [irrespective of del(17p)/*TP53* mutation status; CSLL-D, 2 of 6, page 185; CSLL-D 3 of 6, page 186].

Other Systemic Therapy Regimens

Chemoimmunotherapy regimens including FCR and BR demonstrated activity in patients with relapsed/refractory disease.^{152–154}

HDMP + rituximab was effective in patients with heavily pretreated CLL (including fludarabine refractory disease), although it was associated with infectious complications (including opportunistic fungal infections) in about 30% of patients, which may necessitate adequate anti-infective prophylaxis and close monitoring for early signs of infections.^{155,156}

Lenalidomide ± rituximab also demonstrated activity in patients with relapsed/refractory disease.^{157–159} However, the ORR was lower for lenalidomide + rituximab in the subgroup of patients with fludarabine-refractory CLL compared with those with fludarabine-sensitive CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment.

Alemtuzumab + rituximab results in a higher ORR than that observed with alemtuzumab monotherapy.^{160,161} Myelosuppression and infections were the most common grade 3–4 toxicities. However, it should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.¹⁶² Obinutuzumab (as monotherapy) also demonstrated activity in patients with relapsed/refractory CLL/SLL.¹²²

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

FCR, lenalidomide ± rituximab, obinutuzumab, bendamustine + rituximab (category 2B for patients ≥65 years or patients <65 years with significant comorbidities), and HDMP + anti-CD20 mAb (category 2B) are included as options for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens (CSLL-D, 2 of 6). However, these regimens are not recommended for patients who received these as first-line therapy.

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

Alemtuzumab ± rituximab, HDMP + anti-CD20 mAb, and lenalidomide ± rituximab are included as options for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens (CSLL-D 3 of 6,

page 186). These recommendations are based on results from retrospective analyses or subgroup analyses from prospective clinical trials that had included patients with del(17p) or *TP53* mutation. However, it should be noted that these studies were not sufficiently powered to evaluate the efficacy and safety of regimens in patients with del(17p) or *TP53* mutation.

Special Considerations for the Use of Small-Molecule Inhibitors

Management of Resistance to Small-Molecule Inhibitors

Covalent BTK Inhibitors

Acquired resistance to covalent BTKis is predominantly mediated by *BTK* and *PLCG2* mutations.^{48,163} *BTK* and/or *PLCG2* mutations were detected at an estimated median of 9 months before progression 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.^{48,164} *BTK* C481 mutations were also detected in 69% patients with disease relapse at an estimated median of 12 months before progression in patients treated with acalabrutinib.¹⁶³ Long-term follow-up is needed to confirm if *BTK* C481 mutations will emerge in patients treated with zanubrutinib. Venetoclax is effective for the management of relapsed/refractory CLL after prior treatment with ibrutinib or idelalisib.^{137–143}

Testing for *BTK* mutations may be helpful to confirm resistance to BTKis. The reported VAF are variable, with low VAF often associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance.^{48,164} Testing for *BTK* or *BCL2* 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, including if poor treatment adherence is considered as a possible cause. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment in absence of disease progression.

Alternative covalent BTKi (acalabrutinib or zanubrutinib) is not a reasonable treatment option for patients with a mutation in either *BTK* or *PLCG2*. Pirtobrutinib is an effective option for the management of resistance to covalent BTKi, including in patients with *BTK* C481 mutations.^{133,134} In the BRUIN study, mutations in *BTK*, *TP53*, and *PLCG2* were detected at baseline in 53%, 48%, and 14% of patients, respectively. Among the patients with *BTK* C481 mutation, decrease in *BTK* C481 VAF or complete clearance of *BTK* C481 clone was observed in 86% and 55% of patients, respectively.¹⁶⁵

BCL-2 Inhibitors

Acquisition of *BCL2* mutations (G101V and D103Y) were implicated in resistance to venetoclax.^{166,167} *BCL2* G101V mutation (low VAF) was identified in patients with progressive CLL during venetoclax therapy up to 25 months before clinical progression.¹⁶⁶ *BCL2* mutations are uncommonly associated with clinical resistance to venetoclax; therefore, other resistance mechanisms must be important.

Limited available data suggest that subsequent BTKi therapy or retreatment with venetoclax-based regimens is effective in patients with relapsed CLL after treatment with venetoclax, whereas PI3Ki after fixed-duration treatment with venetoclax does not appear to result in durable remissions.^{144,168–170}

Management of Adverse Events

BTK Inhibitors

Diarrhea, fatigue, arthralgia, infections, cytopenias, bleeding, and cardiovascular toxicities (including atrial fibrillation, ventricular arrhythmias, and hypertension) are adverse events (AEs) associated with BTKis.

AEs associated with BTKi are discussed subsequently and are summarized in Supplementary Table S4.

Acalabrutinib and zanubrutinib both have a more favorable toxicity profile than ibrutinib 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 was lower with acalabrutinib (15% vs 21% for ibrutinib).^{113,171} The incidences of AEs of special interest were also lower with acalabrutinib compared with ibrutinib: atrial fibrillation (9% vs 16%), hypertension (9% vs 23%), and bleeding (38% vs 51%).^{113,171} Acalabrutinib was associated with a higher rate of headache (35% vs 20% for ibrutinib), with only 2% of patients experiencing grade ≥ 3 headache.¹¹³ Headache is commonly observed with acalabrutinib early in the treatment course and can generally be managed with analgesics (eg, acetaminophen) and caffeine supplements and typically subsides with time on treatment.

Zanubrutinib was also associated with a lower rate of atrial fibrillation (grade ≥ 3 ; 2% vs 4%) compared with ibrutinib in the ALPINE trial.¹¹⁶ In contrast, neutropenia of any grade was more frequent with zanubrutinib (29% vs 24% for ibrutinib); however, this did not translate into a higher rate of infection (71% with zanubrutinib vs 73% for ibrutinib). The incidences of grade ≥ 3 infections were 27% and 28%, respectively.

Pirtobrutinib has a favorable toxicity profile (low incidences of atrial fibrillation, major hemorrhage, and hypertension) due to more selective inhibition of BTK and the relative absence of off-target inhibition.^{133,134} Longer-term follow-up data are needed to assess the incidence of these AEs.

The benefit and risk of BTKis should be evaluated in patients requiring antiplatelet or anticoagulant therapies.

Patients requiring the use of anticoagulants including warfarin were excluded from clinical trials evaluating acalabrutinib and ibrutinib while the use of anticoagulants including warfarin was not restricted in clinical trials evaluating zanubrutinib (except in the ALPINE trial). Zanubrutinib can be coadministered with anticoagulants including warfarin. Concomitant administration of ibrutinib or acalabrutinib with warfarin should be avoided.

A baseline assessment of cardiac function should be done before start of covalent BTKi. Hypertension should be managed with antihypertensives as appropriate. Monitoring for signs of bleeding, atrial fibrillation, and hypertension along with appropriate management is recommended for patients receiving BTKis.

Acalabrutinib (tablets) and zanubrutinib can be coadministered with gastric acid-reducing agents (eg, antacids, proton pump inhibitors, H₂-receptor antagonists). Acalabrutinib tablets are the primary formulation and distribution of acalabrutinib capsules was discontinued.

Switching to alternate covalent BTKi therapy can be considered in the setting of nonadherence or intolerance to therapy in the absence of disease progression, especially in patients with atrial fibrillation or hypertension that is not medically controllable. Acalabrutinib and zanubrutinib were shown to be effective for the management of disease in patients with ibrutinib intolerance.^{116,172,173} Pirtobrutinib is also an acceptable option for the management of intolerance to covalent BTKi.^{133,134} Limited data from real-world studies suggest that dose modification of ibrutinib may resolve intolerance without compromising efficacy.^{174–177} In patients with no intolerance, ibrutinib can be continued until disease progression while following recommended dose modification guidance as needed. However, the efficacy of dose modification of ibrutinib was not confirmed in prospective studies.

BCL2 Inhibitor

TLS was an important side effect of venetoclax in early clinical trials. Initiation at 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 is recommended to mitigate the risk and frequency of TLS.¹⁷⁸ Initiation and accelerated dose escalation (20–400 mg over 3 weeks) with close inpatient monitoring for TLS can be done in patients with high tumor burden and concern for rapid disease progression on or after BTKi therapy.^{137,179,180} Recommendations for TLS prophylaxis based on tumor burden are outlined in the algorithm on CSLL-F (page 190).

Other AEs associated with venetoclax ± mAb are summarized in Supplementary Table S5. Growth factor support should be considered for patients with neutropenia. Dose reduction may be necessary for patients with persistent neutropenia and limited bone marrow involvement.

PI3K Inhibitors

Hepatotoxicity (transaminase elevations), severe diarrhea or colitis, pneumonitis, opportunistic infections, and febrile neutropenia were observed in patients treated with idelalisib or duvelisib.

Hepatotoxicity is a major concern in younger patients treated with idelalisib as first-line therapy.¹⁸¹ Close monitoring of transaminase levels is essential, and concurrent administration of idelalisib or duvelisib with other hepatotoxic drugs should be avoided.

The addition of anti-CD20 mAb or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia.¹⁸² Anti-infective prophylaxis for herpes simplex virus and *Pneumocystis jirovecii* pneumonia (PJP), and monitoring for cytomegalovirus reactivation are recommended for patients receiving idelalisib or duvelisib.

Allogeneic Hematopoietic Cell Transplant

Long-term results from several prospective studies showed that allogeneic hematopoietic cell transplant (HCT) can provide long-term disease control and also overcome the poor prognosis associated with del(17p) and *TP53* mutations.^{38,183–189} Available data suggest that CK (≥5 abnormalities) is associated with inferior OS and EFS after allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics.^{190,191}

It is understood that studies involving allogeneic HCT are subject to significant selection biases. Nonetheless, at the present time, given the favorable outcome of patients with del(17p) or *TP53* mutation treated with ibrutinib as first-line therapy and the availability of venetoclax as an effective treatment option for relapsed or refractory CLL, allogeneic HCT is not considered as a reasonable treatment option for relapsed/refractory CLL after initial purine analog-based therapy.¹⁹²

Allogeneic HCT can be considered for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens in patients without significant comorbidities. HCT-specific comorbidity index could be used for the assessment of comorbidities prior to HCT and to predict the risks of nonrelapse mortality and the probabilities of survival after HCT.^{193,194}

Supportive Care

Careful monitoring of AEs after initiation of treatment and supportive care for the treatment related complications (eg, infections, autoimmune cytopenias and viral reactivations) should be an integral part of CLL/SLL management. Patients with bulky lymph nodes, progressive disease after small-molecule inhibitor therapy, and receiving chemoimmunotherapy, venetoclax, lenalidomide, and obinutuzumab are considered to be at high risk for TLS. Treatment-related adverse events should be managed as outlined in the Supportive Care section of the guidelines.

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The NCCN Guidelines Staff have no conflicts to disclose.