



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Version 4.2021 — April 29, 2021

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***William G. Wierda, MD, PhD/Chair † ‡**
The University of Texas
MD Anderson Cancer Center

***John C. Byrd, MD/Vice-Chair ‡ † §**
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Jeremy S. Abramson, MD, MMSc † ‡
Massachusetts General
Hospital Cancer Center

Farrukh Awan, MD † ‡ †
UT Southwestern Simmons
Comprehensive Cancer Center

Syed F. Bilgrami, MD ‡
Yale Cancer Center/
Smilow Cancer Hospital

Greg Bociek, MD, MSc † §
Fred & Pamela Buffett Cancer Center

Danielle Brander, MD ‡
Duke Cancer Institute

Jennifer Brown, MD, PhD ‡
Dana-Farber/Brigham and Women's
Cancer Center

Asher A. Chanan-Khan, MD † ‡
Mayo Clinic Cancer Center

Steve E. Coutre, MD ‡
Stanford Cancer Institute

Randall S. Davis, MD ‡
O'Neal Comprehensive Cancer Center at UAB

Herbert Eradat, MD, MS ‡
UCLA Jonsson Comprehensive Cancer Center

Christopher D. Fletcher, MD ‡
University of Wisconsin
Carbone Cancer Center

Sameh Gaballa MD ‡
Moffitt Cancer Center

Armin Ghobadi, MD ‡ † §
Siteman Cancer Center at Barnes-Jewish
Hospital and Washington University School of
Medicine

Brian Hill, MD, PhD ‡
Case Comprehensive Cancer Center/University
Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

Manali Kamdar, MD ‡
University of Colorado Cancer Center

Lawrence D. Kaplan, MD ‡
UCSF Helen Diller Family
Comprehensive Cancer Center

Nadia Khan, MD †
Fox Chase Cancer Center

Thomas J. Kipps, MD, PhD ‡
UC San Diego Moores Cancer Center

Shuo Ma, MD, PhD †
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Anthony Mato, MD ‡
Memorial Sloan Kettering Cancer Center

Claudio Mosse, MD, PhD ‡
Vanderbilt-Ingram Cancer Center

Stephen Schuster, MD † ‡
Abramson Cancer Center
at the University of Pennsylvania

Mazyar Shadman, MD, MPH † ‡
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Tanya Siddiqi, MD ‡
City of Hope National Medical Center

Deborah M. Stephens, DO ‡
Huntsman Cancer Institute
at the University of Utah

Suchitra Sundaram, MD † ‡
Roswell Park Comprehensive Cancer Center

Nina Wagner-Johnston, MD †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

NCCN
Mary Dwyer, MS
Hema Sundar, PhD

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§ Bone marrow transplantation
‡ Hematology/Hematology oncology
† Internal medicine
† Medical oncology
≠ Pathology/Hematopathology
* Discussion Writing Committee Member



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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/member_institutions.aspx](#).

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2021.



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Updates in Version 4.2021 of the NCCN Guidelines for CLL/SLL from Version 3.2021 include:

[CSLL-F 6 of 6](#)

- Co-administration with CYP3A Inhibitors and Inducers, 2nd bullet was revised: For concomitant use with a ~~moderate or strong CYP3A inhibitor, reduce zanubrutinib dose to 80 mg once daily~~ **strong CYP3A inhibitor, reduce zanubrutinib dose to 80 mg once daily and for concomitant use with a moderate CYP3A inhibitor, reduce zanubrutinib dose to 80 mg twice daily.**

Updates in Version 3.2021 of the NCCN Guidelines for CLL/SLL from Version 2.2021 include:

[CSLL-4](#) and [CSLL-5](#)

- Footnote s was revised: Consider BTK mutation analysis if the patient previously had ibrutinib intolerance and acalabrutinib *or zanubrutinib* use is planned, as patients with BTK mutation are unlikely to respond to acalabrutinib *or zanubrutinib*.

[CSLL-D 4 of 6](#)

- Footnote n was revised: 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.

[MS-1](#)

- The Discussion section has been updated to reflect the changes in the algorithm.
-

Updates in Version 2.2021 of the NCCN Guidelines for CLL/SLL from Version 1.2021 include:

[CSLL-D 2 of 6](#)

- CLL/SLL without del(17p)/TP53 mutation
 - Relapsed/Refractory Therapy was changed to Second-Line and Subsequent Therapy.
 - Second-Line and Subsequent Therapy, Frail patient with significant comorbidity and Patients aged <65 y without significant comorbidities,
 - ◊ Zanubrutinib was added as an option for patients with intolerance or contraindication to other BTKi as a category 2A recommendation; Other recommended regimen.

[CSLL-D 3 of 6](#)

- CLL/SLL with del(17p)/TP53 mutation
 - Relapsed/Refractory Therapy was changed to Second-Line and Subsequent Therapy.
 - First-line therapy,
 - ◊ Zanubrutinib was added as an option for patients with contraindication to other BTKi as a category 2A recommendation; Other recommended regimen.
 - Second-Line and Subsequent Therapy,
 - ◊ Zanubrutinib was added as an option for patients with intolerance or contraindication to other BTKi as a category 2A recommendation; Other recommended regimen.

[Continued](#)



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Updates in Version 1.2021 of the NCCN Guidelines for CLL/SLL from Version 4.2019 include:

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CSLL-1

• Diagnosis, Essential

- ▶ 2nd bullet, 3rd sub-bullet was modified from "CD200 may be useful to distinguish from mantle cell lymphoma (MCL)" to "CD200 positivity may distinguish CLL from mantle cell lymphoma (MCL), which is usually CD200-."
- ▶ 3rd bullet, 1st sub-bullet was modified from "LEF1 may be useful to distinguish from MCL" to "LEF1 expression may distinguish CLL from MCL, which is usually LEF1-."
- ▶ Footnote b was revised, "... should be considered in all cases, ~~and should be done in cases especially for those with an atypical immunophenotype...~~"

CSLL-2

• Workup,

- ▶ Essential, 2nd bullet was revised: "... and direct antiglobulin (Coombs') test."
- ▶ Useful, 8th bullet was revised, "Hepatitis B ~~or~~ and C testing..."

CSLL-3

• Indication present

- ▶ 1st bullet was revised from "Re-evaluate" to "Prior to initiation of treatment, evaluate"
- ▶ 2nd bullet was revised, "IGHV mutation status (if not previously done *when considering chemoimmunotherapy*)."

• Footnotes

- ▶ Footnote l was revised from "Absolute lymphocyte count alone or symptoms related to leukostasis are not an indication for treatment. Leukostasis is rarely seen in patients with CLL" to "Absolute lymphocyte count alone is not an indication for treatment since leukostasis is rarely seen in CLL." (Also for CSLL-4 and CSLL-5)
- ▶ Footnote o was revised from "Re-evaluate when considering treatment with chemoimmunotherapy" to "IGHV mutation status does not change over time and analysis does not need to be repeated if previously done prior to initiation of treatment."

CSLL-4

• CLL/SLL without del(17p)/TP53 mutation

- ▶ Footnote s was added: "Consider BTK mutation analysis if the patient previously had ibrutinib intolerance and acalabrutinib use is planned, as patients with BTK mutation unlikely to respond to acalabrutinib." (Also for CSLL-5)

CSLL-A

• TP53 and Immunoglobulin Heavy-Chain Variable (IGHV) Region Gene Mutation and Surrogates by Flow Cytometry

- ▶ Flow cytometry was removed.

CSLL-C 1 of 4

• Treatment and Viral Reactivation

- ▶ CMV reactivation *in previously infected (seropositive) patients*:
 - ◊ 1st bullet was revised, "Clinicians must be aware of the high risk of cytomegalovirus (CMV) reactivation in patients receiving fludarabine-based chemoimmunotherapy, idelalisib PI3K inhibitors, or alemtuzumab. CMV viremia... ~~polymerase chain reaction (PCR)~~ *quantitation quantitative RT-PCR (qPCR)* at least every 2–3 4 weeks."

CSLL-C 3 of 4

• Non-Melanomatous Skin Cancer

- ▶ 1st bullet, two sub-bullets were added:
 - ◊ Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) were 7 times and 14 times more likely to recur in patients with CLL/SLL than in controls (Mehran K, et al. Dermatol Surg 2005;31:38-42; Mehrany K, et al. Arch Dermatol 2004;140:985-8).
 - ◊ Patients with CLL/SLL are more likely to die from SCC or have metastatic SCC than those without CLL/SLL (Mehran K, et al. J Am Acad Dermatol 2005;53:1067-71)

CSLL-C 4 of 4

• Recurrent Sinopulmonary Infections

- ▶ 2nd bullet, 1st sub-bullet was revised by adding, "Begin monthly *subcutaneous immunoglobulin (SCIG) or* IVIG 0.3–0.5 g/kg."

• Vaccination

- ▶ 3rd bullet was revised, "Pneumococcal *polysaccharide* vaccine (PPSV23) every 5 years."
- ▶ 4th bullet was added, "Zoster vaccine recombinant, adjuvanted for treatment-naïve patients or those treated with BTK inhibitor."

CSLL-D 1 of 6

• CLL/SLL without del(17p)/TP53 mutation, First-line therapy, Frail patient with significant comorbidity...

- ▶ Acalabrutinib ± obinutuzumab was changed from a category 2A recommendation to a category 1 recommendation.
- ▶ Venetoclax + obinutuzumab was changed from a category 2A recommendation to a category 1 recommendation.

• First-line therapy, Patients aged <65 y without significant comorbidities

- ▶ Acalabrutinib ± obinutuzumab was changed from a category 2A recommendation to a category 1 recommendation.

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• Footnote i was modified by adding, "Thompson P, et al. Blood 2016;127:303-309)."

• Footnote q references were changed to "Andritsos L, et al. J Clin Oncol 2008;26:2519-2525; Wendtner C, et al. Leuk Lymphoma 2016;57:1291-1299."

• Footnote r was added, "Not recommended for frail patients."

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UPDATES



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Updates in Version 1.2021 of the NCCN Guidelines for CLL/SLL from Version 4.2019 include:

Histologic Transformation (Richter's) and Progression

HT-1

- Footnote e was revised, "~~IGHV sequencing~~ *Immunoglobulin gene rearrangement* studies of CLL and histologically transformed tissue ~~should be done~~ *may be performed* to establish the clonal relationship."

HT-3

- Richter's transformation, for DLBCL, clonally related or unknown clonal status
 - ▶ Initial therapy, "Suggested treatment regimens" was changed to "Regimens with reported data."
 - ▶ After initial therapy and chemotherapy sensitive, the option was changed to "Consider allogeneic HCT."
- Footnote i was revised by adding, "...and optimal first-line therapy is not established. The regimens listed above are used at NCCN Member Institutions based on published data (See HT-A for references)."

**DIAGNOSIS^a****ESSENTIAL:**

- Hematopathology review of 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 CLL/SLL (biopsy is generally not required)
 - ▶ CLL diagnosis requires presence of monoclonal B lymphocytes $\geq 5 \times 10^9/L$ in peripheral blood
 - ▶ Clonality of B cells should be confirmed by flow cytometry
 - ▶ Adequate immunophenotyping to establish diagnosis by flow cytometry using cell surface markers:^{b,c} kappa/lambda, CD19, CD20, CD5, CD23, CD10; if flow is used to establish diagnosis, also include cytochrome c for cyclin D1 or fluorescence in situ hybridization (FISH) for t(11;14); t(11q;v). CD200 positivity may distinguish CLL from mantle cell lymphoma (MCL), which is usually CD200-.
 - ▶ 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
- If diagnosis is not established by flow cytometry, then proceed with lymph node biopsy. Bone marrow aspirate with biopsy if consult material is nondiagnostic. An FNA or core needle biopsy alone is not generally suitable for the initial diagnosis of lymphoma. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core biopsy and FNA biopsies 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:^b CD3, CD5, CD10, CD20, CD23, cyclin D1. LEF1 expression may distinguish CLL from MCL, which is usually LEF1-.
- Absolute monoclonal B lymphocyte count^c

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:^d

- FISH to detect: +12; del(11q); del(13q); del(17p)
- TP53 sequencing
- CpG-stimulated metaphase karyotype for complex karyotype
- Molecular analysis to detect: *IGHV* mutation status^e

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

^b 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, and 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).

^c Absolute monoclonal B lymphocyte count $< 5000/mm^3$ that persists more than 3 months in the absence of adenopathy or other clinical features of lymphoproliferative disorder is MBL. Cells of 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.

^d [See Prognostic Information for CLL/SLL \(CSLL-A\).](#)

^e *IGHV* mutation status is preferred over flow cytometry. If not available, determination of CD38, CD49d, and ZAP-70 expression by flow cytometry, methylation, or immunohistochemistry may be obtained as surrogate markers for *IGHV* mutation status. Evaluation of these markers can be challenging and is not recommended outside the setting of a clinical trial.

CLL/SLL

[See Workup \(CSLL-2\)](#)

Monoclonal B-cell lymphocytosis (MBL)

- Absolute monoclonal B-lymphocyte count $< 5 \times 10^9/L$
- All lymph nodes < 1.5 cm
- No anemia
- No thrombocytopenia
- No organomegaly
- No constitutional symptoms

→ Observe

Note: All recommendations are category 2A unless otherwise indicated.

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.



WORKUP

ESSENTIAL:

- History and physical exam including measurement of size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- Comprehensive metabolic panel

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct antiglobulin (Coombs) test
- Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated^f
- Beta-2-microglobulin
- Lactate dehydrogenase (LDH)
- Uric acid
- Unilateral bone marrow aspirate + biopsy^g
- Hepatitis B^h and C testing if treatment contemplated
- Multigated acquisition (MUGA) scan/echocardiogram if anthracycline-based regimen is indicated
- Pregnancy testing in women of childbearing age if systemic therapy or RT planned
- Discussion of fertility issues and sperm banking
- PET/CT scan to direct nodal biopsy, if histologic transformation is suspected. [See HT-1.](#)

[SLL/Localized
\(Lugano Stage I\)
\(See CSLL-3\)](#)

[CLL \(Rai Stages 0–IV\)
or
SLL \(Lugano Stage II–IV\)
\(See CSLL-3\)](#)

^f Outside clinical trials, CT scans are not necessary for diagnosis, 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.

^g May be informative for the diagnosis of immune-mediated or disease-related cytopenias.

^h Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, 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 gastroenterologist.

Note: All recommendations are category 2A unless otherwise indicated.

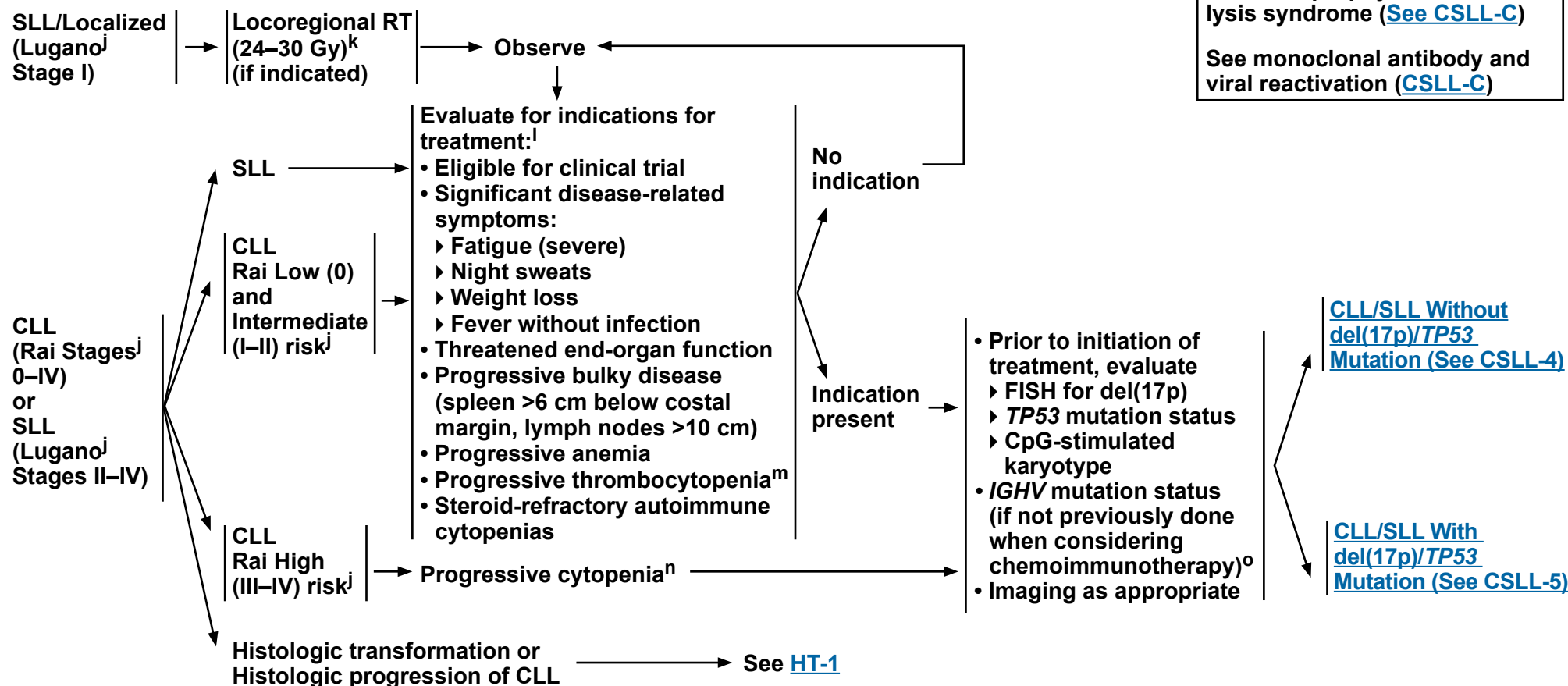
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PRESENTATIONⁱ



Consider prophylaxis for tumor lysis syndrome ([See CSLL-C](#))

See monoclonal antibody and viral reactivation ([CSLL-C](#))

ⁱ See [Supportive Care for Patients with CLL/SLL \(CSLL-C\)](#).

^j See [Rai and Binet Classification Systems \(CSLL-B 1 of 2\)](#) and [Lugano Modification of Ann Arbor Staging System \(CSLL-B 2 of 2\)](#).

^k The dose is delivered in 1.5–2.0 Gy/fraction. See [NCCN Guidelines for B-Cell Lymphomas, Principles of Radiation Therapy](#) for additional details.

^l Absolute lymphocyte count alone is not an indication for treatment since leukostasis is rarely seen in CLL.

^m Platelet counts >100,000 cells/mm³ are typically not associated with clinical risk.

ⁿ Select patients with mild, stable cytopenia (ANC <1000/μL, Hgb <11 g/dL, or platelet <100,000/μL) may continue to be followed with observation.

^o 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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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CLL/SLL WITHOUT DEL(17P)/TP53 MUTATION

FIRST-LINE THERAPYⁱ RESPONSE TO THERAPY

ADDITIONAL THERAPY^s

SECOND-LINE AND SUBSEQUENT THERAPYⁱ

CLL/SLL without del(17p)/TP53 mutation^{i,l,p}

- See Suggested Regimens based on age and functional status ([CSLL-D 1 of 6](#))
- Frail patients with significant comorbidity^q (not able to tolerate purine analogs) OR Patients aged ≥65 y and younger patients with significant comorbidities^q
- Patients aged <65 y without significant comorbidities^q

Response^r

No response

Continue treatment with B-cell receptor (BCR) pathway inhibitor until progression

or
Observation if treated with chemoimmunotherapy or targeted therapy with fixed-duration treatment until indication for retreatment as listed on [CSLL-3](#)

- Re-evaluate
 - FISH for del(17p)
 - TP53 mutation status
 - CpG-stimulated karyotype
 If del(17p)/TP53 mutation, see [CSLL-5](#)
- If histologic transformation or histologic progression of CLL, [see HT-1](#)

- CLL/SLL without del(17p)/TP53 mutation
 - See Suggested Regimens based on age and functional status ([CSLL-D 2 of 6](#))

Clinical trial or Consider allogeneic HCT, if without significant comorbidities^q in patients with CLL refractory to small-molecule inhibitor therapy

Consider prophylaxis for tumor lysis syndrome ([See CSLL-C](#))

See monoclonal antibody and viral reactivation ([CSLL-C](#))

ⁱ See Supportive Care for Patients with CLL/SLL ([CSLL-C](#)).

^l Absolute lymphocyte count alone is not an indication for treatment since leukostasis is rarely seen in CLL.

^p Given incurability with conventional therapy, consider including clinical trial as first-line therapy.

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

^r See Response Definition After Treatment for CLL/SLL ([CSLL-E](#)).

^s Consider BTK mutation analysis if the patient previously had ibrutinib intolerance and acalabrutinib or zanubrutinib use is planned, as patients with BTK mutation are unlikely to respond to acalabrutinib or zanubrutinib.

Note: All recommendations are category 2A unless otherwise indicated.

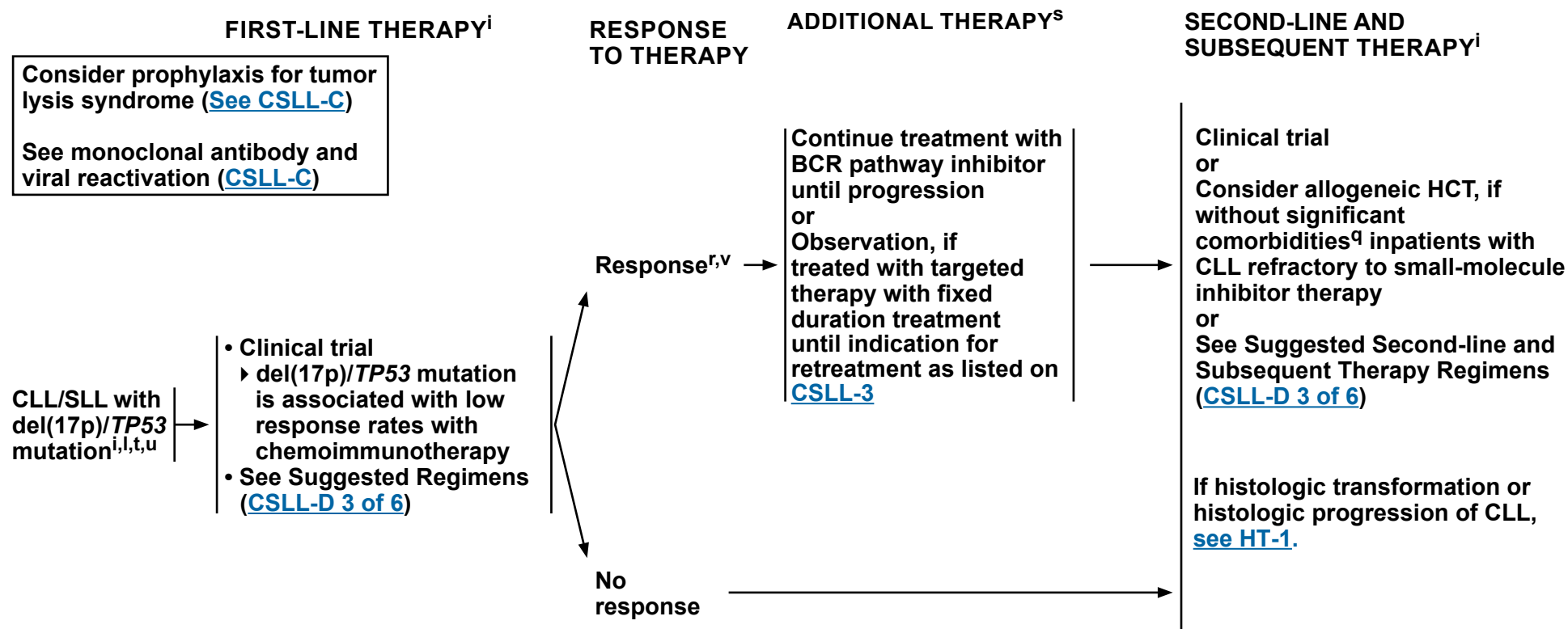
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CLL/SLL WITH DEL(17P)/TP53 MUTATION



ⁱ See Supportive Care for Patients with CLL/SLL ([CSLL-C](#)).

^l Absolute lymphocyte count alone is not an indication for treatment since leukostasis is rarely seen in CLL.

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

^r See Response Definition After Treatment for CLL/SLL ([CSLL-E](#)).

^s Consider *BTK* mutation analysis if the patient previously had ibrutinib intolerance and acalabrutinib or zanubrutinib use is planned, as patients with *BTK* mutation are unlikely to respond to acalabrutinib or zanubrutinib.

^t CPG-stimulated karyotype is useful to identify high-risk patients, particularly for Bruton's tyrosine kinase (BTK) inhibitor therapy.

^u Patients with low percentage of del17p-positive cells should be retested due to chance of false-positive results.

^v For patients with complex karyotype (≥3 abnormalities) achieving remission with or after BTK inhibitor therapy, consider discussion of allogeneic HCT; however, available data do not support this as highly effective (Jagowski S, et al. Br J Haematol 2012;159:82-87).

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PROGNOSTIC INFORMATION FOR CLL/SLL^a

TP53 and Immunoglobulin Heavy-Chain Variable (*IGHV*) Region Gene Mutation

	<u>Favorable</u>	<u>Unfavorable</u>
DNA sequencing^b		
<i>TP53</i>	Wild-type	Mutated
<i>IGHV</i>	>2% mutation	≤2% mutation

Interphase Cytogenetics (FISH)^c

<u>Unfavorable</u>	<u>Neutral</u>	<u>Favorable</u>
del(11q) del(17p)	Normal +12	del(13q) (as a sole abnormality)

Complex Karyotype^d

<u>Unfavorable</u>
≥3 unrelated chromosome abnormalities in more than one cell on karyotype

^a This table provides useful prognostic information for survival and time to progression in patients who received treatment.

^b *IGHV* rearrangements involving VH3-21 carry a poor prognosis even if mutated. *TP53* mutation status also provides additional prognostic information to FISH.

^c 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 chemoimmunotherapy approaches.

^d Complex karyotype is based on results of metaphase karyotyping of CpG-stimulated CLL cells.

Note: All recommendations are category 2A unless otherwise indicated.

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CLL STAGING SYSTEMS

Rai System^a

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood $>5 \times 10^9/L$ clonal B cells and $>40\%$ lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0–I with splenomegaly, hepatomegaly, or both	Intermediate
III ^c	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit $<33\%$	High
IV ^c	Stage 0–III with platelets $<100,000/mm^3$	High

Binet System^b

Stage	Description
A	Hemoglobin ≥ 10 g/dL and Platelets $\geq 100,000/mm^3$ and <3 enlarged areas
B	Hemoglobin ≥ 10 g/dL and Platelets $\geq 100,000/mm^3$ and ≥ 3 enlarged areas
C ^c	Hemoglobin <10 g/dL and/or Platelets $<100,000/mm^3$ and any number of enlarged areas

^a This research was originally published in Blood. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46:219-234. (c) The American Society of Hematology.

^b From: Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.

^c Immune-mediated cytopenias are not the basis for these stage definitions.

Note: All recommendations are category 2A unless otherwise indicated.

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[Continued](#)

CSLL-B
1 OF 2



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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SLL STAGING SYSTEM

Lugano Modification of Ann Arbor Staging System^d (for primary nodal lymphomas)

<u>Stage^e</u>	<u>Involvement^g</u>	<u>Extranodal (E) Status</u>
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky^f	II as above with “bulky” disease	Not applicable
Advanced		
Stage III^h	Nodes on both sides of the diaphragm	Not applicable
	Nodes above the diaphragm with spleen involvement	
Stage IV^h	Additional non-contiguous extralymphatic involvement	Not applicable

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^d Extent of disease is determined by PET/CT for avid lymphomas and CT for non-avid histologies.

^e Categorization of A versus B has been removed from the Lugano Modification of Ann Arbor Staging System.

^f Whether stage II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

^g Note: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

^h Immune-mediated cytopenias are not the basis for these stage definitions.

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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Anti-infective Prophylaxis

- Recommended during treatment and thereafter (if tolerated) for patients receiving purine analog or bendamustine-based chemoimmunotherapy, and/or alemtuzumab
 - Herpes virus prophylaxis with acyclovir or equivalent
 - Pneumocystis jiroveci pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent
- Hepatitis B virus (HBV) and cytomegalovirus (CMV) prophylaxis and monitoring is recommended for high-risk patients. See Treatment and Viral Reactivation below.

Treatment and Viral Reactivation

Hepatitis B virus (HBV):

- Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) testing for all patients receiving anti-CD20 antibody therapy
 - Quantitative hepatitis B viral load by PCR and surface antibody only if one of the screening tests is positive
- Note: Patients receiving IV immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy.
- Prophylactic antiviral therapy with entecavir is recommended for any patient who is HBsAg-positive and receiving treatment. If there is active disease (PCR+), it is considered treatment/management and not prophylactic therapy. In cases of HBcAb positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load.
 - Entecavir is preferred (Huang YH, et al. J Clin Oncol 2013;31:2765-2772; Huang H, et al. JAMA 2014;312:2521-2530.)
 - Avoid lamivudine due to risks of resistance development.
 - Other antivirals including adefovir, telbivudine, and tenofovir are proven active treatments and are acceptable alternatives.

Treatment and Viral Reactivation (continued)

- Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter.
 - ◊ If viral load is consistently undetectable, treatment is considered prophylactic.
 - ◊ If viral load fails to drop or previously undetectable PCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy.
- Maintain prophylaxis up to 12 mo after oncologic treatment ends.
 - ◊ Consult with hepatologist for duration of therapy in patient with active HBV.

Hepatitis C virus (HCV):

- New evidence from large epidemiology studies, molecular biology research, and clinical observation supports an association of HCV and B-cell NHL. Recently approved direct-acting antiviral (DAA) agents for chronic carriers of HCV with genotype 1 demonstrated a high rate of sustained viral responses.
- Low-grade B-cell NHL
 - ◊ According to the American Association for the Study of Liver Diseases, combined therapy with DAA should be considered in asymptomatic patients with HCV genotype 1 since this therapy can result in regression of lymphoma.

CMV reactivation in previously infected (seropositive) patients:

- Clinicians must be aware of the high risk of CMV reactivation in patients receiving PI3K inhibitors or alemtuzumab. The current recommendations for appropriate screening are controversial. CMV viremia should be measured by quantitative RT-PCR (qPCR) at least every 4 weeks. Some clinicians use ganciclovir (oral or IV) pre-emptively if viremia is present; others use ganciclovir only if viral load is rising. Consultation with an infectious disease expert may be necessary.

John Cunningham (JC) virus:

- Progressive multifocal leukoencephalopathy related to JC virus can be seen in patients receiving treatment.

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[Continued](#)



SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Tumor Lysis Syndrome (TLS)

• Laboratory hallmarks of TLS:

- ▶ High potassium
- ▶ High uric acid
- ▶ High phosphorous
- ▶ Low calcium
- ▶ High LDH

• Symptoms of TLS:

- ▶ Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.

• TLS features

- ▶ Consider TLS prophylaxis for patients with the following risk factors:

- ◊ Patients receiving treatment with venetoclax ([See CSLL-G](#)), chemoimmunotherapy, lenalidomide, and obinutuzumab
- ◊ Progressive disease after small-molecule inhibitor therapy
- ◊ Bulky lymph nodes
- ◊ Spontaneous TLS
- ◊ Elevated white blood cell (WBC) count
- ◊ Pre-existing elevated uric acid
- ◊ Renal disease or renal involvement by tumor

• Treatment of TLS:

- ▶ TLS is best managed if anticipated and treatment is started prior to chemotherapy.
- ▶ Centerpiece of treatment includes:
 - ◊ Rigorous hydration
 - ◊ Management of hyperuricemia
 - ◊ Frequent monitoring of electrolytes and aggressive correction (essential)
- ▶ First-line and at retreatment for hyperuricemia
 - ◊ Allopurinol or febuxostat beginning 2–3 days prior to chemotherapy and continued for 10–14 days or
Rasburicase (Doses of 3–6 mg are usually effective.^a One dose of rasburicase is frequently adequate. Redosing should be individualized) is indicated for patients with any of the following risk factors:
 - Urgent need to initiate therapy in a high-bulk patient
 - Situations where adequate hydration may be difficult or impossible
 - Acute renal failure
- ▶ If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

^a There are data to support that fixed-dose rasburicase is very effective in adult patients.

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[Continued](#)

CSLL-C
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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Autoimmune Cytopenias

- Autoimmune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, and direct antiglobulin test (DAT)
 - ▶ AIHA that develops in setting of treatment with fludarabine: Stop, treat, and avoid subsequent fludarabine
- Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets
- Pure red cell aplasia (PRCA): Consider bone marrow evaluation and testing for parvovirus B19, herpes virus, and drug effects
- Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP)

Blood Product Support

- Transfuse according to institutional or published standards.
- Irradiate all blood products to avoid transfusion-associated graft-versus-host disease (GVHD).

Cancer Screening

- Standard screening guidelines should be closely followed for breast, cervical, colon, and prostate cancers.

Non-Melanomatous Skin Cancer

- Patients with CLL/SLL have a higher risk of developing non-melanomatous skin cancers.
 - ▶ Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) were 7 times and 14 times more likely to recur in patients with CLL/SLL than in controls (Mehran K, et al. Dermatol Surg 2005;31:38-42; Mehran K, et al. Arch Dermatol 2004;140:985-988).
 - ▶ Patients with CLL/SLL are more likely to die from SCC or have metastatic SCC than those without CLL/SLL (Mehran K, et al. J Am Acad Dermatol 2005;53:1067-1071).
- Risk factors include caucasians and a history of intensive sun exposure at a young age.
- Annual dermatologic skin screening is recommended.

Rare Complications of Monoclonal Antibody Therapy

- Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur. Consultation with a dermatologist is recommended for management of these complications. Re-challenge with the same monoclonal antibody in such settings is not recommended. It is unclear that re-challenge with alternative CD20 antibodies poses the same risk of recurrence.

Rituximab Rapid Infusion and Subcutaneous Administration

- If no severe infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.
- 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.

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[Continued](#)

CSLL-C
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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Recurrent Sinopulmonary Infections (requiring IV antibiotics or hospitalization)

- Antimicrobials as appropriate
- Evaluate serum IgG, if <500 mg/dL
 - Begin monthly subcutaneous immunoglobulin (SCIG) or IVIG 0.3–0.5 g/kg
 - Adjust dose/interval to maintain nadir level of approximately 500 mg/dL

Thromboprophylaxis

- Recommended for prevention of thromboembolic events in patients receiving lenalidomide:
 - Aspirin 81 mg PO daily if platelets above $50 \times 10^{12}/L$
 - Patients already on anticoagulants, such as warfarin, do not need aspirin
- Note that the above may differ from the [NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease](#) in which the recommendations with lenalidomide pertain only to patients with multiple myeloma

Tumor Flare Reactions

- Management of tumor flare is recommended for patients receiving lenalidomide
- Tumor flare reactions:
 - Painful lymph node enlargement or lymph node enlargement with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash
- Treatment:
 - Steroids (eg, prednisone 25–50 mg PO daily for 5–10 days)
 - Antihistamines for rash and pruritus (cetirizine 10 mg PO once daily or loratadine 10 mg PO daily)
- Prophylaxis:
 - Consider in patients with bulky lymph nodes (>5 cm)
 - Steroids (eg, prednisone 20 mg PO daily for 5–7 days followed by rapid taper over 5–7 days)

Use of Small-Molecule Inhibitors

- [See Special Considerations for the Use of Small-Molecule Inhibitors \(CSLL-F\)](#)

Vaccination

- Avoid all live vaccines
- Annual influenza vaccine^b (live attenuated influenza vaccine should be avoided)
- Pneumococcal polysaccharide vaccine (PPSV23) every 5 years
- Zoster vaccine recombinant, adjuvanted for treatment-naïve patients or those treated with BTK inhibitor

^b In patients who have received rituximab, B-cell recovery occurs by approximately 9 months. Prior to B-cell recovery, patients generally do not respond to influenza vaccine and if given should not be considered vaccinated.

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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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
Frail patient with significant comorbidity (not able to tolerate purine analogs) OR Patients aged ≥65 y and younger patients with significant comorbidities (creatinine clearance [CrCl] <70 mL/min)	<ul style="list-style-type: none"> Acalabrutinib^f ± obinutuzumab (category 1) Ibrutinib^f (category 1) Venetoclax^{f,g} + obinutuzumab (category 1) 	<ul style="list-style-type: none"> Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody^{d,h} (not recommended for frail patients) Chlorambucil + obinutuzumab High-dose methylprednisolone (HDMP) + rituximab (category 2B) Ibrutinib^f + obinutuzumab (category 2B) Obinutuzumab (category 2B) Chlorambucil (category 3) Rituximab (category 3)
Patients aged <65 y without significant comorbidities	<ul style="list-style-type: none"> Acalabrutinib^f ± obinutuzumab (category 1) Ibrutinib^f (category 1) Venetoclax^{f,g} + obinutuzumab 	<ul style="list-style-type: none"> Bendamustine + anti-CD20 monoclonal antibody^{d,h,i} FCR (fludarabine,^j cyclophosphamide, rituximab)^{i,k} (preferred for patients with <i>IGHV</i>-mutated CLL) FR (fludarabine^j + rituximab)^{k,l} HDMP + rituximab (category 2B) Ibrutinib^f + rituximab (category 2B) PCR (pentostatin, cyclophosphamide, rituximab) (category 3)

POST FIRST-LINE CHEMOIMMUNOTHERAPY MAINTENANCE THERAPY

Other recommended regimen

- Consider lenalidomide for high-risk patients (blood MRD ≥10⁻² or ≥10⁻⁴ and <10⁻² with unmutated *IGHV*)^m after first-line therapy

Consider prophylaxis for tumor lysis syndrome ([See CSLL-C](#))
 See monoclonal antibody and viral reactivation ([See CSLL-C](#))

[See Footnotes on CSLL-D 4 of 6](#)

[See Suggested Regimens for Second-line and Subsequent Therapy for CLL/SLL without del\(17p\)/TP53 mutation \(2 of 6\)](#)

[See Suggested Regimens for CLL/SLL with del\(17p\) \(3 of 6\)](#)

Note: All recommendations are category 2A unless otherwise indicated.

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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SUGGESTED TREATMENT REGIMENS^{a,b,c,d} CLL/SLL without del(17p)/TP53 mutation (alphabetical by category)

SECOND-LINE AND SUBSEQUENT THERAPY ^e		
Frail patient with significant comorbidity OR Patients aged ≥65 y and younger patients with significant comorbidities (CrCl <70 mL/min)	Preferred regimens	Other recommended regimens
	<ul style="list-style-type: none"> • Acalabrutinib^{f,n} (category 1) • Ibrutinib^f (category 1) • Venetoclax^{f,g} + rituximab (category 1) • Duvelisib^f • Idelalisib^f + rituximab^o 	<ul style="list-style-type: none"> • Alemtuzumab^p ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR^{j,k} • HDMP + rituximab • Idelalisib^f • Lenalidomide^q ± rituximab • Obinutuzumab • Ofatumumab • Reduced-dose PCR • Venetoclax^{f,g} • Zanubrutinib (for patients with intolerance or contraindication to other BTKi)ⁿ • Dose-dense rituximab (category 2B) • Bendamustine + rituximab^r (category 2B) • Bendamustine, rituximab + ibrutinib^{f,r} (category 2B) • Bendamustine, rituximab + idelalisib^{f,r} (category 3)
Patients aged <65 y without significant comorbidities	Preferred regimens <ul style="list-style-type: none"> • Acalabrutinib^{f,n} (category 1) • Ibrutinib^f (category 1) • Venetoclax^{f,g} + rituximab (category 1) • Duvelisib^f • Idelalisib^f + rituximab^o 	Other recommended regimens <ul style="list-style-type: none"> • Alemtuzumab^p ± rituximab • Bendamustine + rituximab • FCI^{j,k} + ofatumumab • FCR^{j,k} • HDMP + rituximab • Idelalisib^f • Lenalidomide^q ± rituximab • Obinutuzumab • Ofatumumab • PCR • Venetoclax^{f,g} • Zanubrutinib (for patients with intolerance or contraindication to other BTKi)ⁿ • Bendamustine, rituximab + ibrutinib^f (category 2B) • Bendamustine, rituximab + idelalisib^f (category 2B)

POST SECOND-LINE CHEMOIMMUNOTHERAPY MAINTENANCE THERAPY (for complete or partial response after second-line therapy)

Other recommended regimens

- Lenalidomide^m
- Ofatumumab (category 2B)

Consider prophylaxis for tumor lysis syndrome ([See CSLL-C](#))
See monoclonal antibody and viral reactivation ([See CSLL-C](#))

[See Footnotes on CSLL-D 4 of 6](#)

[See Suggested Regimens for CLL/SLL with del\(17p\) \(3 of 6\)](#)

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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SUGGESTED TREATMENT REGIMENS^{a,b,c,d} CLL/SLL with del(17p)/*TP53* mutation (alphabetical by category)

FIRST-LINE THERAPY ^e	
<u>Preferred regimens</u>	<u>Other recommended regimens</u>
<ul style="list-style-type: none"> • Acalabrutinib^f ± obinutuzumab • Ibrutinib^f • Venetoclax^{f,g} + obinutuzumab 	<ul style="list-style-type: none"> • Alemtuzumab^p ± rituximab • HDMP + rituximab • Obinutuzumab • Zanubrutinib (for patients with contraindication to other BTKi)ⁿ
SECOND-LINE AND SUBSEQUENT THERAPY ^e	
<u>Preferred regimens</u>	<u>Other recommended regimens</u>
<ul style="list-style-type: none"> • Acalabrutinib^{f,n} (category 1) • Ibrutinib^f (category 1) • Venetoclax^{f,g} + rituximab (category 1) • Duvelisib^f • Idelalisib^f + rituximab^o • Venetoclax^{f,g} 	<ul style="list-style-type: none"> • Alemtuzumab^p ± rituximab • HDMP + rituximab • Idelalisib^f • Lenalidomide^q ± rituximab • Ofatumumab^s • Zanubrutinib (for patients with intolerance or contraindication to other BTKi)ⁿ

Consider prophylaxis for tumor lysis syndrome ([See CSLL-C](#))
 See monoclonal antibody and viral reactivation ([See CSLL-C](#))

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

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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

^a See references for regimens [CSLL-D 5 of 6](#) and [CSLL-D 6 of 6](#).

^b See [Supportive Care for Patients with CLL/SLL \(CSLL-C\)](#).

^c Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route.

^d Re-challenge with the same monoclonal antibody is not recommended in patients experiencing rare complications (eg, mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis). It is unclear whether re-challenge with alternative anti-CD20 antibodies poses the same risk of recurrence.

^e An FDA-approved biosimilar is an appropriate substitute for rituximab.

^f See [Special Considerations for the Use of Small-Molecule Inhibitors \(CSLL-F\)](#).

^g See [Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden \(CSLL-G\)](#).

^h Anti-CD20 monoclonal antibodies include: rituximab, ofatumumab, or obinutuzumab.

ⁱ Data from the CLL10 study confirm the superiority of FCR over bendamustine + rituximab (BR) in younger patients. For patients >65 y, the outcome was similar for both regimens with less myelosuppression and infection for BR. FCR was associated with improved PFS (with a plateau in PFS beyond 10-year follow-up) in patients with mutated *IGHV* without del(17p)/*TP53* mutation (Thompson P, et al. Blood 2016;127:303-309).

^j See [Discussion](#) for further information on oral fludarabine.

^k 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.

^l Not recommended for CLL with del(11q). Outcomes for CLL with del(11q) are better with chemoimmunotherapy containing an alkylating agent.

^m Minimal residual disease (MRD) evaluation with a sensitivity of 10⁻⁴ according to the standardized ERIC method or standardized next-generation sequencing (NGS) method.

ⁿ Acalabrutinib or zanubrutinib has not been shown to be effective for ibrutinib-refractory CLL with *BTK* C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib or zanubrutinib without recurrence of symptoms.

^o Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or NCI CTCAE grade ≥3 neutropenia or grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).

^p 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 \(CSLL-C 1 of 4\)](#).

^q 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.

^r Not recommended for frail patients.

^s This is not effective in patients with lymph nodes >5 cm.

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**SUGGESTED TREATMENT REGIMENS**
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Note: All recommendations are category 2A unless otherwise indicated.**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.[Continued](#)**CSLL-D**
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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SUGGESTED TREATMENT REGIMENS

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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

RESPONSE DEFINITION AFTER TREATMENT FOR CLL/SLL^a

Parameter	CR	PR	PD ^b	SD
Group A				
Lymph nodes	None ≥ 1.5 cm	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	$\geq 1500/\mu\text{L}$	$\geq 1500/\mu\text{L}$ or $>50\%$ improvement over baseline		

Minimal Residual Disease (MRD) Assessment:

- Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of treatment is an important predictor of treatment efficacy.^{e,f,g}
- 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} .^{h,i} Next-generation DNA sequencing (NGS)-based assays have been shown to be more sensitive, thus allowing for the detection of MRD at the level of 10^{-6} .^{i,j,k}
- MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized NGS method.

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.

[Footnotes on CSLL-E 2 of 2](#)

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RESPONSE DEFINITION AFTER TREATMENT FOR CLL/SLL^{a,b}

- ^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.
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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS¹

ACALABRUTINIB	CSLL-F 1 of 6
DUVELISIB	CSLL-F 2 of 6
IBRUTINIB	CSLL-F 3 of 6
IDELALISIB	CSLL-F 4 of 6
VENETOCLAX	CSLL-F 5 of 6
ZANUBRUTINIB	CSLL-F 6 of 6

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS¹

ACALABRUTINIB

Dosage

- The recommended dose of acalabrutinib is 100 mg PO BID administered continuously until progression of disease or development of side effects that require dose reduction or cessation of therapy.

Lymphocytosis

- Early lymphocytosis is expected with acalabrutinib therapy and is not considered a sign of progression but rather an on-target effect of the drug. Additionally, patients who have been on acalabrutinib and then have their medication held can have a small node or lymphocytosis flare. Re-initiation of therapy generally is effective in this setting.

Toxicity

- No ≥grade 3 bleeding events occurred in the initial trial and subsequent studies have had a low frequency of this. Grade ≥3 hypertension and atrial fibrillation were observed in 3% and 2% of patients, respectively. Monitor for atrial fibrillation/hypertension and manage as appropriate.
- Acalabrutinib may increase the risk of hemorrhage in patients receiving anti-platelet or anticoagulant therapies. Trials with acalabrutinib excluded patients receiving warfarin. Patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3 days pre-and post-surgery depending on the type of surgery and risk of bleeding.
- Headaches are commonly observed with acalabrutinib early in therapy and typically resolve with time over 1–2 months of therapy. These generally can be managed with analgesics such as acetaminophen and caffeine supplements.

Resistance

- At time of disease progression on acalabrutinib, transition to next therapy as soon as possible upon stopping acalabrutinib since progression may accelerate when acalabrutinib is stopped. Treatment-free interval should be as short as possible.
- Testing for *BTK* and *PLCG2* mutations may be useful in patients receiving acalabrutinib and suspected of having progression. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment.

Co-administration with CYP3A Inhibitors and Inducers

- Avoid concomitant use of strong CYP3A inhibitors or inducers.
- For strong CYP3A inhibitors used short-term, interrupt acalabrutinib during the duration of inhibitor use.
- For concomitant use with a moderate CYP3A inhibitor, reduce acalabrutinib dose to 100 mg once daily.
- If concomitant use with a strong CYP3A inducer cannot be avoided, increase acalabrutinib dose to 200 mg twice daily.

Co-administration with Gastric Acid-Reducing Agents

- Avoid coadministration with proton pump inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids.

¹ Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

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[Continued](#)

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS¹

DUVELISIB

Dosage

- The recommended dose of duvelisib is 25 mg PO twice daily, per prescribing recommendations.

Lymphocytosis

- Upon initiation of duvelisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of duvelisib therapy and may persist for several weeks on treatment.

Toxicity

- **Hepatotoxicity:** Monitor hepatic function prior to and during treatment. Interrupt if ALT/AST >5 x ULN (upper limit of normal) and when resolved resume at the same dose (25 mg twice daily) for first occurrence or at a reduced dose (15 mg twice daily) for subsequent occurrence. Discontinue duvelisib if ALT/AST > 20 × ULN.
- **Diarrhea or colitis:** Monitor for the development of severe diarrhea or colitis. Initiate supportive therapy with antidiarrheal agents as appropriate. In case of severe diarrhea or colitis, interrupt duvelisib until resolution and then resume at a reduced dose (15 mg twice daily) or discontinue duvelisib. Severe diarrhea and colitis can be managed with enteric acting steroids (eg, budesonide) or systemic steroids.
- **Pneumonitis without suspected infectious cause:** Interrupt duvelisib and treat with systemic steroid therapy for grade 2. If pneumonitis recovers to grade 0 or 1, duvelisib may be resumed at reduced dose (15 mg twice daily). Discontinue duvelisib if non-infectious pneumonitis recurs or patient does not respond to steroid therapy or for severe (grade 3) or life-threatening pneumonitis.
- **Cutaneous reactions:** Monitor closely and initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids. In case of severe cutaneous reactions, interrupt duvelisib until resolution and initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids. Resume at a reduced dose (15 mg twice daily). If severe cutaneous reaction does not improve, worsens, or recurs, discontinue duvelisib.
- **Infections:** PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent is recommended during treatment and until the absolute CD4+ T-cell count is >200 cells/μL.
- **CMV reactivation:** Consider prophylactic antivirals to prevent CMV infection including CMV reactivation. [See CSLL-C.](#)

Co-administration with CYP3A Inhibitors and Inducers

- Avoid concomitant use of strong CYP3A inducers.
- Patients taking concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of duvelisib toxicity. Reduce dose to 15 mg twice daily when coadministered with strong CYP3A4 inhibitors.
- Monitor for signs of toxicities when coadministering with sensitive CYP3A substrates.

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[Continued](#)

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NCCN Guidelines Version 4.2021

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS¹

IBRUTINIB

Dosage

- The recommended dose of ibrutinib is 420 mg PO daily, administered continuously until progression of disease.

Lymphocytosis

- Upon initiation of ibrutinib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and may persist for several weeks on treatment.

Toxicity

- Grade >2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded patients on concurrent warfarin. Ibrutinib should be held 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure. Ibrutinib should not be given concomitantly with warfarin.
- New-onset atrial fibrillation was reported in 6%–9% of patients, and was associated with ibrutinib administration.
 - ▶ Consider non-warfarin anticoagulation
 - ▶ Monitor carefully
 - ▶ If uncontrolled, consider switching to alternate therapy
 - ▶ If switching to venetoclax, assess risk for TLS ([See CSLL-G](#))
- Hypertension associated with ibrutinib has been uncommonly reported as a basis for discontinuation and should be managed with anti-hypertensives as appropriate. Ibrutinib should only be discontinued for uncontrollable hypertension.
- Grade ≥3 ventricular tachyarrhythmias were reported in 0.2% of patients on ibrutinib.
 - ▶ Periodically monitor patients for cardiac arrhythmias.
 - ▶ Obtain an ECG for patients who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest pain) or new-onset dyspnea.
 - ▶ Manage cardiac arrhythmias appropriately.
 - ▶ Consider the benefit-risk of ibrutinib in patients with persistent cardiac arrhythmias and follow dose modification guidelines.
- Invasive fungal infections have rarely been reported early after ibrutinib initiation on treatment. There currently is no recommendation for routine prophylaxis.

Resistance

- At time of disease progression on ibrutinib, transition to next therapy as soon as possible upon stopping ibrutinib since progression may accelerate when ibrutinib is stopped. Treatment-free interval should be as short as possible.
- Testing for *BTK* and *PLCG2* mutations may be useful in patients receiving ibrutinib and suspected of having progression. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment.

Co-administration with CYP3A Inhibitors and Inducers

- Avoid concomitant use of ibrutinib with strong or moderate inhibitors of CYP3A.
 - ▶ For strong CYP3A inhibitors used short-term (eg, antifungals and antibiotics for 7 days or less; eg, ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting ibrutinib therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically.
 - ▶ If a moderate CYP3A inhibitor must be used, reduce the ibrutinib dose.
 - ▶ Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of toxicity associated with ibrutinib therapy.
- Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, St. John's Wort). Consider alternative agents with less CYP3A induction.

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[Continued](#)

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS¹

IDELALISIB

Dosage

- The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.

Lymphocytosis

- Upon initiation of idelalisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of idelalisib therapy and may persist for several weeks on treatment.

Toxicity

- **Hepatotoxicity:** Monitor hepatic function prior to and during treatment. Interrupt if ALT/AST >5 x ULN and when resolved may resume at a reduced dose (100 mg PO twice daily).
- **Diarrhea or colitis:** Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.
- **Pneumonitis:** Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.
- **Intestinal perforation:** Discontinue idelalisib if intestinal perforation is suspected.
- **CMV reactivation:** [See CSLL-C.](#)
- **Infections:** PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent.

Co-administration with CYP3A Inhibitors and Inducers

- **Avoid concomitant use of strong CYP3A inhibitors or inducers.**
- **Patients taking concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of idelalisib toxicity.**

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**SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS¹****VENETOCLAX****Dosage**

- The recommended dose of venetoclax is 400 mg PO daily until disease progression or unacceptable toxicity.
- Initiate venetoclax at 20 mg for one week and gradually escalate to target dose of 400 mg PO daily over 5 weeks to reduce the risk of TLS.^{2,3} See [CSLL-G](#) for recommended TLS prophylaxis and monitoring based on tumor burden.
- Consider re-initiating at a lower dose then continue with dose escalation in patients who have treatment interruption for >1 week during escalation.
- Initiation and accelerated escalation of venetoclax (20–400 mg over 3 weeks) with close inpatient TLS monitoring can be done in the subgroup of patients with high tumor burden and where there is concern for rapid disease progression on or following BTK inhibitor therapy. For accelerated escalation, venetoclax is administered at 20 mg on Week (W)1/Day (D)1; 50 mg on W1/D2–3; 100 mg on W1/D4–7 (all inpatient), then outpatient unless concern for TLS; 200 mg on W2/D1–7; and 400 mg on W3/D1–continuous.^{4,5} This accelerated schedule has been explored in a small number of patients, and they were hospitalized and received intensive monitoring and prophylaxis. Additionally, continued BTK inhibition concurrent with initiation and escalation of venetoclax with discontinuation of BTK inhibitor when up to the venetoclax 400 mg daily dose can be considered. These agents can be given together safely.

Toxicity

- Consider the use of neutrophil growth factors for neutropenia according to standard guidelines. Dose reduction may be necessary for persistent neutropenia and limited bone marrow involvement with CLL.
- Reduced renal function (CrCl <80 mL/min) increases the risk of TLS. Perform tumor burden assessments, including CT scan and blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with venetoclax. See [CSLL-G](#) for recommended TLS prophylaxis and monitoring based on tumor burden.

Co-administration with CYP3A Inhibitors and Inducers

- Avoid concomitant use of strong CYP3A inhibitors or inducers.

¹ Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

² Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol* 2018;19:65-75.

³ Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood* 2018;131:1704-1711.

⁴ Davids M, Jones J, Eradat H, et al. Modified venetoclax dose ramp-up in select high-risk patients with chronic lymphocytic leukemia (CLL) with progression after B-cell receptor pathway inhibitors (BCRi) [abstract]. *Clinical Lymphoma, Myeloma & Leukemia* 2017;17:S302.

⁵ Koenig K, Konstantinou D, Rogers A, et al. Rapid dose escalation of venetoclax in patients with chronic lymphocytic leukemia previously treated with B-cell receptor inhibitor therapy [abstract]. *EHA Congress* 2018:Abstract PF357.

Note: All recommendations are category 2A unless otherwise indicated.

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS¹

ZANUBRUTINIB

Dosage

- The recommended dose of zanubrutinib is 160 mg orally twice daily or 320 mg orally once daily, administered continuously until progression of disease or development of side effects that require dose reduction or cessation of therapy.

Lymphocytosis²

- Transient treatment-related lymphocytosis was observed in most patients, which does not signify disease progression.

Toxicity²

- Grade ≥ 3 major bleeding events were reported in 5% of patients treated with zanubrutinib monotherapy. Consider the benefit-risk of zanubrutinib in patients requiring anti-platelet or anticoagulant therapies. Consider withholding zanubrutinib for 3–7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- Atrial fibrillation and atrial flutter occurred in 3% of patients treated with zanubrutinib monotherapy. Grade 3 or higher atrial fibrillation and atrial flutter were reported in 2% of patients treated with zanubrutinib monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Monitor for atrial fibrillation and atrial flutter and manage appropriately.
- Grade 1 or 2 anemia (4%) or thrombocytopenia (6%) and grade 3 or higher adverse events including neutropenia (14%), infections (14%) and hypertension (3%) were reported in patients treated with zanubrutinib monotherapy.
- Consider prophylaxis for herpes simplex virus, PJP, and other infections according to standard of care in patients who are at increased risk for infections.

Co-administration with CYP3A Inhibitors and Inducers

- Avoid concomitant use of moderate or strong CYP3A inducers.
- For concomitant use with a strong CYP3A inhibitor, reduce zanubrutinib dose to 80 mg once daily and for concomitant use with a moderate CYP3A inhibitor, reduce zanubrutinib dose to 80 mg twice daily.

Co-administration with Gastric Acid-Reducing Agents

- No clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid reducing agents (proton pump inhibitors, H₂-receptor antagonists).

¹ Please refer to package insert for full prescribing information and monitoring for adverse reactions, available at www.fda.gov.

² Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. Haematologica 2020;Online ahead of print.

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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 x10 ⁹ /L	<ul style="list-style-type: none"> • Oral hydration (1.5–2 L) • Allopurinol^d 	Outpatient <ul style="list-style-type: none"> • 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 x10 ⁹ /L	<ul style="list-style-type: none"> • Oral hydration (1.5–2 L) and consider additional intravenous hydration • Allopurinol 	Outpatient <ul style="list-style-type: none"> • 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 x10 ⁹ /L AND any lymph node ≥5 cm	<ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • Pre-dose, 4, 8, 12, and 24 hours Outpatient at subsequent ramp-up doses <ul style="list-style-type: none"> • Pre-dose, 6–8 hours, 24 hours

^a Prescribing information for venetoclax. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.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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Histologic Transformation (Richter's) and Progression

DIAGNOSIS

ESSENTIAL:

- An FNA alone is not suitable for the initial diagnosis of histologic transformation. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core needle biopsy and FNA biopsies in conjunction with appropriate ancillary techniques for the differential diagnosis (ie, IHC, flow cytometry) may be sufficient for diagnosis.
- Perform excisional biopsy, if lymph node is accessible. Core needle biopsy is acceptable when a lymph node is not easily accessible. Biopsy the lesion with highest standardized uptake value (SUV) on PET scan.
- Perform hematopathology review of all slides with at least one paraffin block representative of the tumor. Bone marrow aspirate with biopsy if consult material is nondiagnostic.
 - ▶ Diffuse large B-cell lymphoma (DLBCL): Sheets of confluent large B cells that are not part of a proliferation center are sufficient to diagnose a Richter's transformation to DLBCL.^{a,b,c}
 - ▶ Classical Hodgkin lymphoma (CHL): Rare transformation to CHL demonstrates large Reed-Sternberg (RS) cells that express CD30, CD15, and PAX-5 but lack strong, uniform CD20 and CD45 (also lack co-expression of both OCT-2 and BOB.1). The background lymphocytes in those CHL cases are CD3+ T cells with a varying degree of admixed eosinophils, histiocytes, and plasma cells.^d

→ [See Workup \(HT-2\)](#)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- FISH to detect +12; del(11q); del(13q); del(17p)
- CpG-stimulated metaphase karyotype for complex karyotype
- Molecular analysis to establish clonal relatedness between CLL and DLBCL cells^e
- TP53 sequencing

^a While occasionally an increase in proliferative rate can be shown with Ki-67, this is not considered diagnostic of a transformation.

^b Proliferation centers in CLL may express c-MYC and/or cyclin D1. This does not change the diagnosis.

^c First, "CLL with expanded proliferation centers" or "accelerated CLL" may be diagnosed in cases where proliferation centers in CLL are expanded or fuse together (>20x field or 0.95 mm²) AND show Ki-67 proliferative rate >40% or >2.4 mitoses/proliferation center. Second, progression to "CLL with increased polymphocytes" or "CLL/PLL" may occur when there are increased polymphocytes in the blood (>10%–<55%). Neither of these findings should be considered a transformation event, but rather as progression of CLL. B-PLL should be reserved for the diagnosis of de novo leukemias that are not associated with CLL.

^d If morphologic RS cells are identified but the background cells are still the B cells of CLL, an EBV stain such as EBER should be performed. EBV infection of CLL can produce RS-like proliferations, but the background cells are still CLL and not the reactive mix typically seen in Hodgkin lymphoma. These cases should NOT be considered a Richter's transformation event.

^e Immunoglobulin gene rearrangement studies of CLL and histologically transformed tissue may be performed to establish the clonal relationship.

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Histologic Transformation (Richter's) and Progression

WORKUP

ESSENTIAL:

- History and physical exam with attention to node-bearing areas, including Waldeyer's ring, and the size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- Comprehensive metabolic panel
- LDH, uric acid
- Whole body PET/CT scan or chest/abdomen/pelvis CT with contrast of diagnostic quality
- Epstein-Barr virus (EBV) evaluation by EBV-LMP1 or EBER-ISH

USEFUL IN SELECTED CASES:

- Unilateral bone marrow aspirate and biopsy
- MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated
- Hepatitis B^f and C testing
- Pregnancy testing in women of childbearing age
- Discussion of fertility issues and sperm banking
- Human leukocyte antigen (HLA) typing

[Richter's Transformation \(HT-3\)](#)

[CLL with Progression \(HT-3\)](#)

^f Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy) [See Treatment and Viral Reactivation \(CSLL-C 1 of 4\)](#). Tests include 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 gastroenterologist.

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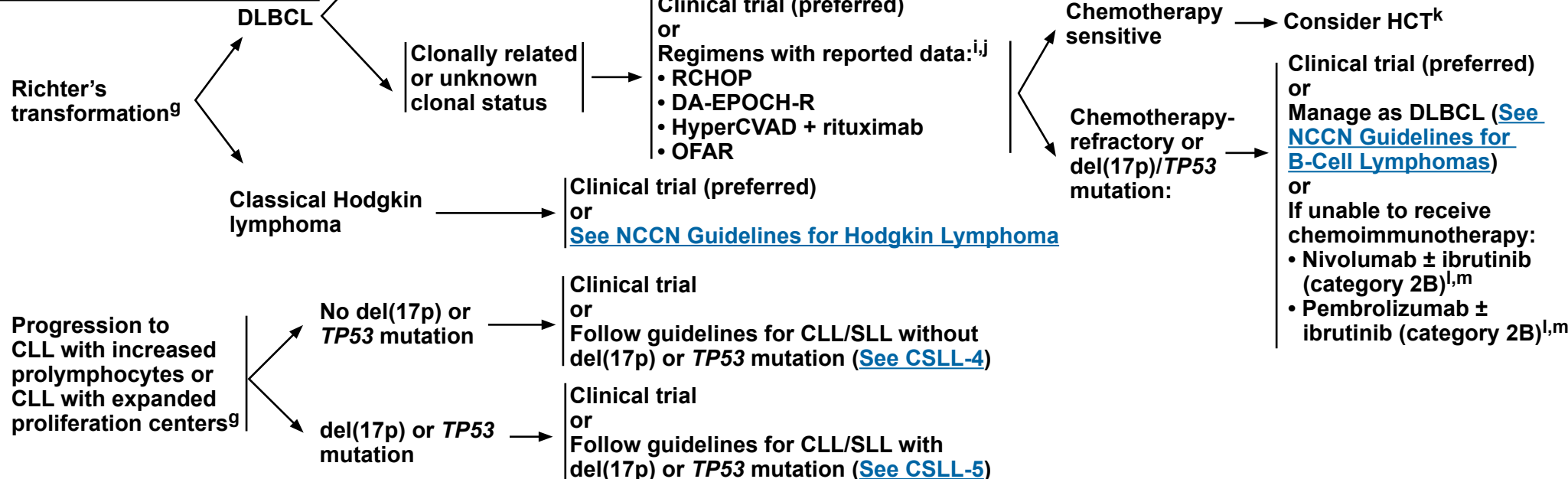


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Histologic Transformation (Richter's) and Progression

CLINICAL PRESENTATION^h

Consider prophylaxis for tumor lysis syndrome ([See CSLL-C](#))
See monoclonal antibody and viral reactivation ([See CSLL-C](#))



^g "Accelerated CLL," "CLL with expanded proliferation centers," and "CLL-PLL or CLL with increased prolymphocytes" (defined on [HT-1](#)) are not considered Richter's transformation, but are associated with more aggressive disease and poorer outcome [Gine E, et al, Haematologica 2010;95(9):1526-1533; Ciccone M, et al, Leukemia 2012;26:499-508; Swerdlow S, et al. 2017 WHO Classification]. Optimal management for these cases has not been established.

^h For T-cell prolymphocytic leukemia, see [NCCN Guidelines for T-Cell Lymphomas](#).

ⁱ Richter's transformation to DLBCL (clonally related or unknown clonal status) is generally managed with treatment regimens recommended for DLBCL. However, these regimens typically result in poor responses and optimal first-line therapy is not established. The regimens listed above are used at NCCN Member Institutions based on published data (See [HT-A](#) for references).

^j 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. An FDA-approved biosimilar is an appropriate substitute for rituximab.

^k Cwynarski K, et al. J Clin Oncol 2012;30:2211-2217.

^l See [Special Considerations for the Use of Small-Molecule Inhibitors \(CSLL-F\)](#).

^m The panel acknowledged that there is a paucity of data for the use of these regimens in patients with Richter's transformation refractory to chemotherapy or in patients with a del(17p)/TP53 mutation; however, these regimens may be considered given the limited options available for this patient population. Additional data will be forthcoming.

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SUGGESTED TREATMENT REGIMENS

DA-EPOCH-R

Rogers KA, Huang Y, Ruppert A, et al. A single-institution retrospective cohort study of first-line R-EPOCH chemoimmunotherapy for Richter syndrome demonstrating complex chronic lymphocytic leukaemia karyotype as an adverse prognostic factor. *Br J Haematol* 2018;180:259-266.

HyperCVAD + rituximab

Tsimberidou AM, Kantarjian HM, Cortes J, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. *Cancer* 2003;97:1711-1720.

Tsimberidou AM, O'Brien S, Khouiri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol* 2006;24:2343-2351.

OFAR

Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's syndrome or fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol* 2008;26:196-203.

Tsimberidou AM, Wierda WG, Wen S, et al. Phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab therapy in aggressive relapsed/refractory chronic lymphocytic leukemia or Richter syndrome. *Clin Lymphoma Myeloma Leuk* 2013;13:568-574.

RCHOP

Tsimberidou AM, O'Brien S, Khouiri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol* 2006;24:2343-2351.

Nivolumab

Jain N, Ferrajoli A, Basu S, et al. A Phase II trial of nivolumab combined with ibrutinib for patients with Richter transformation [abstract]. *Blood* 2018;132:Abstract 296.

Younes A, Brody J, Carpio C, et al. Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia: a phase 1/2a study. *Lancet Haematol* 2019;6:e67-e78.

Pembrolizumab

Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood* 2017;129:3419-3427.

Rogers KA, Huang Y, Dotson E, et al. Use of PD-1 (PDCD1) inhibitors for the treatment of Richter syndrome: experience at a single academic centre. *Br J Haematol* 2019;185:363-366.

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

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

All recommendations are considered appropriate.

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Discussion

This discussion corresponds to the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.
Last updated: March 11, 2021.

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Overview

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are characterized by a progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. Morphologically, these leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or prolymphocytes. CLL remains the most prevalent adult leukemia in Western countries. In 2021, an estimated 21,250 people will be diagnosed with CLL in the United States, and an estimated 4,320 people will die from the disease.¹ CLL and SLL are different manifestations of the same disease and are managed in much the same way.² The major difference is that in CLL, a significant number of the abnormal lymphocytes are found in the peripheral blood in addition to 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 the peripheral blood.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for CLL/ SLL, an electronic search of the PubMed database was performed to obtain key literature in Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma published since the previous Guidelines update using the following search terms: chronic lymphocytic leukemia/small lymphocytic lymphoma, Richter syndrome, and histologic transformation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.³

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV;

Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Staging

The Rai and Binet systems are the two staging systems currently used for the evaluation of patients with CLL, both in the routine practice and clinical trial settings.^{4,5} Both staging systems rely on physical evidence (ie, presence of lymph node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden.

The modified Rai classification stratifies patients into three risk groups: low-risk disease (Rai stage 0), intermediate-risk disease (Rai stage I–II), and high-risk disease (Rai stage III–IV) with median survival times of 150 months, 71 to 101 months, and 19 months, respectively.⁴

The Binet staging system stratifies patients into three prognostic groups based on the number of involved areas and the level of hemoglobin and platelets and, similar to the Rai staging system, provides meaningful correlation with clinical outcome.⁵

The Lugano Modification of the Ann Arbor Staging System is used for patients with SLL.⁶



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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Prognostic Factors

Immunoglobulin Heavy Chain Variable Region (*IGHV*) Gene Mutation

IGHV mutation status is an important predictor of survival outcomes. Unmutated *IGHV* ($\geq 98\%$ homology with germline gene sequence) is associated with poor prognosis and significantly decreased survival compared with mutated *IGHV*, irrespective of the stage of the disease.^{7,8} 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).⁹ Unmutated *IGHV* or the *VH3-21* gene usage was shown to be an independent predictor of shorter treatment-free interval and/or survival outcomes, even when high-risk genetic abnormalities were included in the multivariable regression models.¹⁰⁻¹³

IGHV mutation status is a predictor of high response rates and improved overall survival (OS) in patients treated with FCR (fludarabine, cyclophosphamide, and rituximab).¹⁴⁻¹⁶ In the CLL8 trial (FCR vs. FC [fludarabine/cyclophosphamide] as first-line therapy), FCR was associated with significantly longer progression-free survival (PFS; median not reached compared to 42 months for FC; $P < .001$) and OS (5-year OS rate was 86% compared to 80% for FC) in the subgroup of patients with *IGHV*-mutated CLL.¹⁴ The survival benefit was seen across all cytogenetic subgroups including del(11q), except for patients with del(17p) and normal karyotype. However, the *IGHV* mutation status did not have an impact on overall response rate (ORR) in this trial. In a phase II study of 300 patients with previously untreated CLL, minimal residual disease (MRD) negativity was achieved in 51% of patients with mutated *IGHV*, with a PFS rate of 80% at 13 years.¹⁵ In a multivariable analysis, unmutated *IGHV* and del(17p) by conventional karyotyping were significantly associated with inferior PFS. Long-term PFS was notable particularly for patients with mutated *IGHV*, with a plateau on the PFS curve beyond 10 years. In the CLL10 study that evaluated FCR versus bendamustine/rituximab (BR) as

first-line therapy for CLL without del(17p), the PFS benefit of FCR was significant in physically fit patients less than 65 years and in patients with mutated *IGHV*.¹⁶ Among patients with a mutated *IGHV*, the median PFS was not reached for FCR compared to 55 months for BR ($P = .089$).

Cytogenetic Abnormalities

Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) are present in more than 80% of patients with previously untreated CLL. 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.¹⁷

Del(13q) as a sole abnormality is associated with favorable prognosis and the longest median survival (133 months). Del(11q) is often associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 months).¹⁷ The addition of an alkylating agent to fludarabine-based chemoimmunotherapy may help to overcome the adverse prognostic significance of del(11q) in patients with previously untreated CLL.^{13,18} Del(17p), which reflects the loss of the *TP53* gene and is frequently associated with mutations in the remaining *TP53* allele, is associated with short treatment-free interval, short median survival (32 months), and poor response to chemotherapy.¹⁷ *TP53* abnormalities can occur in the absence of del(17p) and *TP53* mutations have been identified as predictors of resistance to fludarabine-based or bendamustine-based regimens and poor survival, independent of 17p chromosome status.¹⁹⁻²²

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 during the course of treatment.²³ The prognostic significance of del(17p) may be dependent on the proportion of



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malignant cells with this abnormality, and the prognosis is more favorable when the percentage of cells with del(17p) is low.^{13,24,25}

In the CLL4 trial (chlorambucil vs. fludarabine vs. FC as first-line therapy), the loss of *TP53* was found to be the strongest predictor of poor outcomes to first-line therapy.¹³ In addition, del(11q) and treatment allocation were independent predictors for PFS and age was an independent predictor for OS. In the long-term follow-up from the CALGB 9712 study (concurrent vs. sequential fludarabine and rituximab as first-line therapy), del(17p) or del(11q) were independent predictors for shorter survival.²⁶

Cell Surface Markers

Among the cell surface markers detected by flow cytometry, immunohistochemistry, or methylation (CD38, CD49d, and ZAP-70), CD49d (≥30%) is the strongest predictor of OS and treatment-free survival.²⁷⁻³¹ CD38 expression (≥30%)^{7,11,13,32-34} and/or ZAP-70 (≥20%) are associated with shorter PFS and OS outcomes.³⁵⁻⁴⁰ In addition, it was suggested that ZAP-70 positivity may be a stronger predictor of clinical outcomes than *IGHV* mutation status or CD38.³⁸⁻⁴⁰ ZAP-70 methylation (which is closely associated with ZAP-70 expression and *IGHV* mutation status) was also reported to be a useful prognostic test for patients with CLL but is not routinely performed clinically.⁴¹⁻⁴³

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.^{44,45} However, it is influenced in a CLL disease-independent manner by renal dysfunction.

Prognostic Models

Several prognostic models incorporating traditional and newer prognostic markers have been developed for the risk stratification.⁴⁶⁻⁵¹

A prognostic nomogram and a more simplified prognostic index were developed using age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes to help stratify patients with untreated CLL into three different risk groups (low, intermediate, and high).⁴⁶ The estimated median survival times were not reached—10 years and 5 years—respectively, for the three risk groups. 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.⁴⁶ Several studies have independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in patients with untreated CLL, including those with early-stage (Rai stage 0) disease.^{47,48}

In another prognostic model, increased size of cervical lymph nodes, three involved nodal sites, del(17p) or del(11q), unmutated *IGHV* status, and elevated serum LDH levels were identified as independent predictors of shorter time to first treatment.⁴⁹ This model may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention.

Integrated CLL Scoring System (ICSS) stratifies patients into three risk groups (low, intermediate, and high) based on the cytogenetic abnormalities detected by FISH, *IGHV* mutation status, and CD38 expression.⁵⁰ International prognostic index for CLL (CLL-IPI) stratifies patients into four risk groups (low, intermediate, high, and very high) based on *TP53* and *IGHV* mutation status, serum beta-2 microglobulin concentration, clinical stage, and age.⁵¹ The 5-year OS rates were



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significantly different between these risk groups (93%, 79%, 63%, and 23%, respectively). CLL-IPI has been validated in an independent cohort of patients with newly diagnosed CLL and is also useful for predicting time-to-first treatment and risk of progression in patients receiving first-line chemoimmunotherapy.⁵² International Prognostic Score for Early-stage CLL (IPS-E) has been proposed (based on the analysis of individual patient data an international cohort of 4,933 patients) to predict the likelihood of treatment requirement in patients with early-stage CLL.⁵³ IPS-E score stratifies patients with early-stage CLL into 3 risk groups with significantly different time to first treatment (TTFT). The cumulative risk for the need of treatment after 1 and 5 years of observation was 14% and 61%, respectively, for IPS-E high-risk patients compared to 2% and 28%, for intermediate-risk patients and <0.1% and 8% for low-risk patients. These findings need to be validated in a prospective clinical trial.

Recurrent mutations in *NOTCH1*, *SF3B1*, and *BIRC3* genes with prognostic implications have been identified in approximately 4% to 15% of patients with newly diagnosed CLL and the incidences are much higher (15%–25%) in patients with fludarabine-refractory CLL.^{54–59} An integrated prognostic model including *NOTCH1*, *SF3B1*, and *BIRC3* mutations along with the cytogenetic abnormalities detected by FISH has been proposed to classify patients into four 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].⁶⁰ The 10-year survival rates for the four subgroups were 29%, 37%, 57%, and 69%, respectively.

Early progression of disease (POD) within 2 years of first-line therapy has been identified as a prognostic factor for inferior clinical outcomes in patients with CLL.⁶¹ In an analysis of 829 patients, early POD after first-line treatment was associated with unfavorable cytogenetics (del 11q or del 17p) and inferior ORR to first-line treatment. The ORR was 53% for

those with early POD compared to 80% and 84%, respectively, for those with late POD and no POD. Early POD was also associated with inferior OS across all patients and in patients treated with chemoimmunotherapy (FCR or BR; $P < .05$).

Collectively, data from above studies suggest that the prognostic significance of aforementioned prognostic markers may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated. In addition, the survival estimates for traditional as well as the newer prognostic markers were generated in an era of chemotherapy or chemoimmunotherapy. Newer small-molecule inhibitor-based therapy has significantly improved survival outcomes, including patients with high-risk disease. The duration of follow-up is short in many of these studies and the prognostic significance of these markers in patients treated with newer targeted therapies is uncertain.

More recently, two prognostic models have been developed to predict the outcome of patients treated with targeted therapy.^{62,63} The first prognostic model stratified patients treated with ibrutinib into three risk groups (high [3–4 points]; intermediate [2 points] and low [0 points]) based on the *TP53* aberrations, prior treatment, beta-2 microglobulin (≥ 5 mg/L), and LDH > 250 U/L.⁶² The 3-year PFS rates were 47%, 74%, and 87% for the high-, intermediate-, and the low-risk group, 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. Another validated prognostic model has been reported to predict OS in patients with relapsed or refractory CLL treated with chemoimmunotherapy and targeted therapies (ibrutinib, idelalisib, and venetoclax) and.⁶³ This prognostic model stratifies patients into three risk groups (low [score 0–1]; intermediate [score 2–3] and high risk [score 4]) using serum beta-2 microglobulin (≥ 5 mg/dL), elevated LDH, hemoglobin



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(<110 g/L for women or <120 g/L for men), and time from initiation of last therapy (<24 months). This model allows for the identification of high-risk patients with previously treated CLL who do not achieve a good outcome with available targeted therapies.

Complex Karyotype

Complex karyotype (CK; ≥ 3 unrelated chromosomal abnormalities in more than one cell on CpG-stimulated karyotype of CLL cells) may be a stronger predictor of poor clinical outcomes than del(17p) or *TP53* mutation in patients with CLL treated with ibrutinib-based regimens.⁶⁴⁻⁶⁷ In a multivariate analysis, among patients with relapsed/refractory CLL treated with ibrutinib-based regimens, only CK was significantly associated with inferior event-free survival (EFS; $P = .006$), whereas CK ($P = .008$) and fludarabine-refractory CLL ($P = .005$) were independently associated with inferior OS.⁶⁴ In another analysis of 308 patients treated with ibrutinib on four sequential clinical trials, in a multivariate analysis, CK at baseline, presence of del(17p), and age less than 65 years were all independently associated with a risk for CLL progression.⁶⁸ In patients 65 years and older without CK or del(17p), the estimated cumulative incidence of CLL progression at 4 years was 2% compared to 44% in patients less than 65 years with CK and del(17p). A more recent retrospective analysis of greater than 5,000 patients with available cytogenetic data suggests that CK is associated with variable clinical behavior.⁶⁷ 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 (three unrelated chromosomal abnormalities) and intermediate CK (four unrelated chromosomal abnormalities) were clinically relevant only if coexisting with *TP53* aberrations.

Response Criteria

The response criteria developed by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) are outlined in CSLL-E. 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.⁶⁹

Immunomodulating agents such as lenalidomide can result in a tumor flare reaction characterized by painful enlargement of lymph nodes, lymphocytosis, rash, and bone pain. Tumor flare reaction correlated with clinical response in patients with CLL treated with lenalidomide.⁷⁰

B-cell receptor (BCR) pathway inhibitor (BCRi) therapy with Bruton's tyrosine kinase inhibitors (BTKi; ibrutinib and acalabrutinib) and phosphatidylinositol 3-kinase inhibitors (PI3Ki; idelalisib and duvelisib) cause early mobilization of lymphocytes into the blood 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.⁷¹

Considering these findings, the IWCLL response criteria were revised to more precisely predict the outcome of patients with CLL treated with immunomodulating agents and BCRi.⁷² The revised IWCLL response criteria allow for a new response category, "partial response (PR) with lymphocytosis (PR-L)," for patients receiving BTKi (ibrutinib or acalabrutinib) or PI3Ki (idelalisib or duvelisib) to include clinical response (reduction in lymph nodes and splenomegaly) with persistent lymphocytosis (in the absence of other indicators of progressive disease).



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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

Undetectable minimal residual disease (uMRD; $<10^{-4}$ detectable leukemic cells in peripheral blood or bone marrow) after the end of treatment (EOT) with chemoimmunotherapy⁷³⁻⁷⁶ or fixed duration treatment venetoclax-based regimens⁷⁷⁻⁸⁰ is emerging as an important predictor of treatment efficacy.

In the combined analysis of two randomized phase III studies conducted by the German CLL Study Group (GCLLSG) (CLL8 and CLL10), MRD status at the end of chemoimmunotherapy correlated with better survival in a multivariate analysis.⁷³ Among patients who achieved complete response (CR) and PR, PFS was longer for those with MRD-negative CR and MRD-negative PR (61 months and 54 months, respectively) than those with MRD-positive CR and MRD-positive PR (35 months and 21 months, respectively).⁷³ The persistence of post-treatment splenomegaly as a sole abnormality in MRD-negative patients did not have a negative impact on PFS. In a prospective study of 289 patients with CLL, uMRD at the end of first-line chemoimmunotherapy with FCR correlated with longer PFS.⁷⁴ The median PFS was not reached for patients with uMRD compared to 38 months for those with detectable MRD ($P < .001$). MRD level ($\leq 1\%$ vs. $> 1\%$) after three 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 three courses of FCR (median 73 months vs. 41 months, $P < .001$), but similar for $< 0.01\%$ versus 0.01% – 1% .

The uMRD (in the peripheral blood) after the EOT with fixed duration venetoclax-based regimens also translated into improved PFS regardless

of the clinical response status among patients with newly diagnosed as well as relapsed/refractory CLL.⁷⁷⁻⁸⁰ In the CLL14 study, the rate of uMRD in the peripheral blood at EOT was significantly higher with venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab (74% vs. 34%; $P < .0001$).^{77,78} The 2-year PFS rate for venetoclax + obinutuzumab was higher (93% vs. 37%) for patients with uMRD (MRD levels $\leq 10^{-5}$) compared to those with detectable MRD (MRD level $> 10^{-2}$).⁷⁸ In the MURANO study, the rate of uMRD at the EOT with venetoclax + rituximab (VenR) was 62% compared to 13% after EOT with BR and the rate of uMRD as best MRD response at any time during the study was also higher with VenR (83% vs. 23%).⁷⁹ The 5-year follow-up data from the MURANO study also showed that uMRD at the EOT with VenR was associated with improved OS.⁸⁰ The estimated 3-year survival rate was 95% for patients who had uMRD without PD at the EOT compared to 85% for those with MRD at the EOT. Unmutated *IGHV*, del(17p) and genomic complexity (≥ 3 copy number variations) were associated with higher rates of MRD conversion and subsequent progressive disease after attaining uMRD at EOT whereas *TP53*, *NOTCH1*, and *BIRC3* mutations were associated with lower rates of uMRD among patients treated with VenR.^{80,81}

These findings support the integration of MRD assessment as part of response evaluation. 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} .^{82,83} Next-generation DNA sequencing (NGS)-based assays have been reported to be more sensitive allowing for the detection of MRD at the level of 10^{-6} .⁸³⁻⁸⁶

Diagnosis

The diagnosis of CLL requires the presence of at least $5 \times 10^9/L$ monoclonal B-lymphocytes in the peripheral blood and the clonality of B



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cells should be confirmed by flow cytometry.⁶⁹ The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with less than $5 \times 10^9/L$ B-lymphocytes in the peripheral blood.⁶⁹ 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 effacement of the lymph node architecture is observed in biopsy samples.

Flow cytometry of peripheral blood with immunophenotyping using cell surface markers is adequate for the diagnosis of CLL, and 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, and IHC for left ventricular ejection fraction 1 (LEF1) may be helpful in the differential diagnosis of CLL, especially to exclude other CD5+ B-cell lymphoproliferative disorders—specifically mantle cell lymphoma.⁸⁷⁻⁹⁰

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 FISH is difficult in CLL due to the very low *in vitro* proliferative activity of the leukemic cells. CpG oligonucleotide stimulation can be utilized to enhance metaphase cytogenetics.^{91,92}

Molecular analysis for *IGHV* mutation status is preferred over flow cytometry. *IGHV* mutation testing is recommended based on reproducibility and ready availability. A variety of *IGHV* mutation percentage cut-off levels ranging from 1% to 5% have been studied.⁹³ In a retrospective analysis of 203 patients treated with the FCR regimen, higher cut off levels were incrementally associated with favorable PFS and

OS, suggesting that *IGHV* mutation percentage is a continuous variable in patients treated with the FCR regimen.⁹⁴ A cut-off level of 2% or less *IGHV* mutation is routinely used in clinical practice to differentiate patients with *IGHV*-mutated CLL from those with *IGHV*-unmutated CLL.^{95,96} Patients with *IGHV*-mutated CLL by this definition can have long-term progression-free survival following FCR (54% at 13 years).¹⁵ *IGHV* mutation status is necessary when considering treatment with chemoimmunotherapy.

CD38, CD49d, and ZAP-70 expression correlate with unmutated *IGHV*, and these have been proposed as surrogate markers for *IGHV* mutation status.^{7,28,35,36} However, discordant results between *IGHV* mutation status and CD38 or ZAP-70 positivity have been reported in about 20% to 28% of cases.^{13,38,97} Furthermore, standardization and reproducibility of these markers across laboratories remains a challenge. Evaluation of CD38, CD49d, and ZAP-70 is not recommended outside the context of clinical trials.

Monoclonal B-cell Lymphocytosis

Monoclonal B-cell lymphocytosis (MBL) is a condition in which an abnormal B-cell population with immunophenotype of CLL or related low-grade lymphoproliferative disorder but does not meet the diagnostic criteria for CLL.^{98,99} An absolute monoclonal B-lymphocyte count of $<5 \times 10^9/L$ 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.¹⁰⁰

MBL is further categorized into low-count MBL ($<0.5 \times 10^9/L$) that rarely progresses to CLL and high-count MBL ($>0.5 \times 10^9/L$) that progresses to CLL requiring therapy at a rate of 1% to 2% per year.^{101,102} High-count MBL is distinguished from Rai 0 CLL based on whether the monoclonal



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B-cell count is above or below $5 \times 10^9/L$.¹⁰³ A nodal variant characterized by nodal infiltration of CLL-line cells without apparent proliferation centers and absence of lymphadenopathy has also been described in a subset of patients with MBL.¹⁰⁴

MBL is associated with favorable molecular characteristics, mutated *IGHV* and del(13q), lower prevalence of del(11q)/del(17p) and mutated *TP53*, slower lymphocyte doubling time, longer treatment-free survival, and very low rate of progression to CLL.⁹⁹ Observation is recommended for all individuals with MBL.

Workup

The workup for CLL/SLL is similar to the workup for other lymphoid neoplasms. Quantitative immunoglobulins may be informative in patients with recurrent infections. Measurement of beta-2 microglobulin may provide useful prognostic information.⁴⁶ Reticulocyte counts and a direct Coombs test should be performed to evaluate for the possibility of hemolysis and pure red cell aplasia (PRCA) in patients with anemia.

The prognostic significance of bone marrow involvement (diffuse vs. nodular) is no longer a factor with the availability of more reliable prognostic markers that can be obtained by analysis of circulating lymphocytes (eg, *IGHV* mutation status and cytogenetic abnormalities detected by FISH). Thus, bone marrow biopsy ± aspirate is no longer considered a required part of the diagnostic evaluation of patients with suspected CLL, but it may be informative for the diagnosis of immune-mediated or disease-related cytopenias prior to initiation of treatment.

CT scans may be useful for the evaluation of symptoms or bulky disease, to monitor disease progression in patients with new symptoms when peripheral adenopathy is not present or for the assessment of tumor lysis syndrome (TLS) risk category prior to the initiation of

venetoclax. However, serial CT scans are not recommended for asymptomatic patients. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.^{105,106}

Biosimilars

A biosimilar is a biological product that is highly similar to the FDA-approved reference biological product with the exception of minor differences in clinically inactive components and no clinically meaningful differences in safety, purity, or potency.¹⁰⁷

Pharmacokinetic (drug exposure) and pharmacodynamic (response) studies in the appropriate patient population are essential to demonstrate the efficacy and safety of the biosimilar.¹⁰⁸ Biosimilars require only one clinical trial to demonstrate equivalent safety and efficacy in the most sensitive indication for the reference biological product. If the mechanism of action, pharmacokinetics, and pharmacodynamics are similar, the biosimilar may be approved for all of the same indications as the reference biological product and can be substituted for the reference biological product.¹⁰⁸

Extrapolation of clinical and safety data from one indication to other approved indications is a key concept in the development of biosimilars that potentially provides substantial cost savings in oncology care, as biosimilars are typically more affordable than their reference products. Extrapolation should only be considered for indications where the mechanism of action is identical to that studied in the pivotal trial.

Alternating between the biosimilar and the reference product is acceptable without the intervention of a health care provider only if a biosimilar is designated as interchangeable since such a substitution will not result in higher toxicity or diminished efficacy.¹⁰⁷ However, alternating



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between the biosimilar and reference product is not recommended, if the biosimilar is not designated as interchangeable.

The guidelines recommend the use of an FDA-approved biosimilar as an appropriate substitute for rituximab. The approval is based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic data, clinical immunogenicity data, and other clinical data that demonstrate these are biosimilar to rituximab in terms of safety and efficacy. These biosimilars have not been approved as interchangeable biological products. Therefore, during a single course of therapy, the patient should remain on the same product that was used to initiate treatment throughout the course of the treatment.

Localized SLL (Lugano stage I)

Locoregional radiation therapy (RT; 24–30 Gy) is an appropriate induction therapy for patients with symptomatic localized disease. 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 has progressed after initial RT should be treated as described below 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 the absence of disease symptoms, a “watch and wait” approach is often appropriate for patients with stage II–IV SLL, low-risk CLL (Rai stage 0 or Binet A), or intermediate-risk CLL (Rai stage I–II or Binet B) and treatment will be beneficial if they become symptomatic or show evidence of progressive disease.⁶⁹ Patients with advanced-stage or high-risk CLL (Rai stage III–IV or Binet C) with progressive cytopenia require treatment. Selected patients with mild, stable cytopenia may

continue to be observed. In a randomized prospective phase III study of patients with early-stage high-risk CLL, although FCR resulted in high ORR (93%) and significantly prolonged EFS (median not reached vs. 19 months; $P < .001$) compared to watch and wait, there was no significant OS benefit (5-year OS rate was 83% with FCR compared to 80% for watch and wait).¹⁰⁹ These results confirm that “watch and wait” remains an appropriate treatment options for selected patients with early-stage high-risk CLL.

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.⁶⁹ Absolute lymphocyte count alone is not an indication for treatment and symptoms related to leukostasis are exceedingly rare in CLL patients.⁶⁹

In patients with indications for initiating treatment, patient age, performance status or fitness, and the presence or absence of del(17p) or *TP53* mutation should then help to direct treatment options, as discussed below. Re-evaluation for *TP53* mutation status and del(17p) by FISH, and *IGHV* mutation status if not previously done (important for selection of initial treatment when considering chemoimmunotherapy) are recommended prior to initiating treatment. CpG-stimulated karyotyping is useful to identify high-risk patients, particularly for treatment with targeted agents.

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 clinical trials, including the studies conducted by the GCLLSG.¹¹⁰ Comorbidities are frequently present in older patients and the presence of



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multiple comorbidities (≥ 2 comorbidities) was an independent predictor of clinical outcome, independent of patients' age or disease stage.¹¹¹ In a multivariate analysis, after adjustment for other prognostic factors and treatment, comorbidity maintained independent prognostic value. These findings underscore the need to assess comorbidities, in addition to patient age and performance status, prior to treatment selection.

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.^{111,112} In the CLL14 study, CIRS score greater than 6 or an estimated CrCl less than 70 mL/min was used as the eligibility criteria for patients with significant comorbidities.^{77,113}

Patients are stratified into three groups based on their functional status and presence or absence of comorbidities: frail patients with significant comorbidities, patients 65 years or older or younger patients with significant comorbidities (CrCl < 70 mL/min), and patients less than 65 years without significant comorbidities.

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

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

The efficacy data (ORR, PFS, and OS) from selected randomized clinical trials that have evaluated small-molecule inhibitors and chemoimmunotherapy as first-line therapy are summarized in [Table 1](#).

First-line Therapy: Preferred Regimens

Acalabrutinib ± Obinutuzumab

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 trial.¹¹⁴ Acalabrutinib + obinutuzumab was associated with a PFS benefit in patients with *IGHV*-unmutated CLL as well as *IGHV*-mutated CLL compared to chlorambucil + obinutuzumab. This study, however, was not powered to compare the PFS benefit between the two acalabrutinib arms. The estimated 2-year OS rates were 95%, 95%, and 92%, respectively. There was a trend towards improved OS for acalabrutinib ± obinutuzumab, despite crossover for disease progression in the chlorambucil + obinutuzumab arm, though longer follow-up is needed to confirm any OS benefit.

Acalabrutinib ± obinutuzumab was initially included with a category 2A recommendation for all patients with CLL without del(17p) or *TP53* mutation. After re-review of the data from the full publication, the panel consensus was to change the recommendation to category 1.

Ibrutinib

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 in patients 65 years or older without del(17p).¹¹⁵ In this study, after a median follow-up of 5 years, ibrutinib resulted in significantly higher ORR ($P < .0001$) and significantly longer PFS rate ($P < .0001$) compared to chlorambucil. 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 to 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*.



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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*. The presence of CK did not have an impact on PFS among patients treated with ibrutinib.²² The estimated 2-year PFS rates were 91% and 87%, respectively, for ibrutinib and ibrutinib + rituximab among patients with CK.

The panel consensus was to continue the listing of ibrutinib with a category 1 recommendation for frail patients with significant comorbidities (not able to tolerate purine analogs) and for patients 65 years or older or younger patients with significant comorbidities.

The ECOG-ACRIN cancer research group (E1912) study showed that ibrutinib + rituximab was more effective than FCR for patients 70 years or younger without del(17p)/*TP53* mutation, especially in patients with unmutated *IGHV*.¹¹⁶ These results suggest that ibrutinib may be an appropriate option (instead of chemoimmunotherapy) for younger patients with *IGHV* unmutated CLL who do want to enroll in a clinical trial. Therefore, based on the results of the E1912 study, the panel consensus was to change the recommendation of ibrutinib from a category 2A to category 1 recommendation for patients less than 65 years without del(17p) or *TP53* mutation.

Venetoclax + Obinutuzumab

Venetoclax in combination with obinutuzumab was granted broad FDA approval for the treatment of patients with previously untreated and relapsed/refractory CLL. In the CLL14 study, there was no difference in PFS between treatment groups for patients with mutated *IGHV* and the undetectable MRD rate at EOT was significantly higher with venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab.^{77,113}

Venetoclax + obinutuzumab was also associated with low rate of conversion to MRD-positive status 1 year after treatment. The panel

consensus was to include venetoclax + obinutuzumab as a preferred regimen with a category 2A recommendation for frail patients with significant comorbidities (not able to tolerate purine analogs) and patients 65 years or older or younger patients with significant comorbidities based on the results of the CLL14 study.^{77,113}

The CLL14 study established the efficacy of this combination only in patients with comorbidities (CIRS score >6 or an estimated CrCl <70 mL/min).^{77,113} The panel members acknowledged that the efficacy of this combination in patients without significant comorbidities has not been established in a randomized clinical trial. However, with the recent FDA approval, some panel members agreed that venetoclax + obinutuzumab may be an appropriate fixed-duration chemotherapy-free treatment option for younger patients without comorbidities who do want to enroll in a clinical trial. Therefore, initially, the consensus of the panel was to include venetoclax + obinutuzumab as an option under “other recommended regimens” with a category 2B recommendation for patients less than 65 years of age without significant comorbidities. After re-review of the data from the CLL14 study (following the publication of the full paper), the panel consensus was to change the recommendation of venetoclax + obinutuzumab from category 2B (other recommended regimen) to category 2A (preferred regimen) for patients less than 65 years of age without significant comorbidities.

First-Line Therapy: Other Recommended Regimens

Bendamustine + Anti-CD20 Monoclonal Antibody

In the CLL10 study, there was no significant difference in PFS between BR and FCR as first-line therapy for CLL without del(17p), in patients greater than 65 years, although the PFS benefit of FCR was significant in physically fit patients less than 65 years.¹¹⁷ The incidence of severe neutropenia and infections was significantly more frequent in the FCR arm, especially among patients greater than 65 years. The updated results



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of the CLL10 study also confirmed that BR is associated with a decreased risk of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).¹¹⁷ After a median follow-up of 58 months, the incidences of secondary AML and MDS were significantly higher in the FCR arm (7% for patients >65 years and 3% in patients <65 years) compared to BR (1% for both older and younger patients).

Bendamustine + anti-CD20 monoclonal antibody (mAb) may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is included as an option for patients 65 years or older or younger patients with significant comorbidities and for patients less than 65 years without significant comorbidities.¹¹⁷⁻¹²⁰

Chlorambucil + Obinutuzumab

The CLL11 study established that chlorambucil + obinutuzumab is superior to chlorambucil + rituximab for elderly patients and for those with comorbidities lacking del(17p) or *TP53* mutation.¹²¹

The results of the iLLUMINATE study demonstrated ibrutinib + obinutuzumab as a more effective first-line therapy than chlorambucil + obinutuzumab for patients 65 years or older and for patients less than 65 years with comorbidities (median age was 71 years; ibrutinib + obinutuzumab, n = 113; chlorambucil + obinutuzumab, n = 116).¹²²

Based on the results of the iLLUMINATE study, the panel consensus was to change the recommendation of chlorambucil + obinutuzumab from category 1 (preferred regimen) to category 2A (other recommended regimen) for frail patients with significant comorbidities and patients 65 years or older or younger patients with significant comorbidities.

Chlorambucil + rituximab or ofatumumab is no longer recommended as an option for first-line therapy for this group of patients based on the results of the CLL11 study that established the superiority of

chlorambucil + obinutuzumab over chlorambucil + rituximab for elderly patients and for those with comorbidities.

Fludarabine, Cyclophosphamide, and Rituximab

The panel emphasizes that FCR is the preferred first-line therapy option for *IGHV*-mutated CLL in patients less than 65 years without significant comorbidities since the FCR regimen results in high response rates and improved OS in this specific subgroup of patients with previously untreated CLL.^{14,15,117}

The E1912 study showed that ibrutinib + rituximab was more effective than FCR for patients 70 years or less without del(17p)/*TP53* mutation.¹¹⁶ Based on the results of the E1912 study, the panel consensus was to change the recommendation of FCR from category 1 (preferred regimen) to category 2A (other recommended regimen) for patients less than 65 years without significant comorbidities.

An oral formulation of fludarabine is approved by the FDA for the treatment of patients with CLL that has not responded to or has progressed during or after treatment with at least one standard alkylating-agent-containing regimen.¹²³⁻¹²⁵ However, the efficacy and safety of the oral formulation compared with IV fludarabine has not been established in prospective randomized trials. Therefore, the NCCN Guidelines cannot recommend the appropriate use of oral fludarabine at this time.

Fludarabine + Rituximab

Fludarabine + rituximab (FR) is included as an option for patients less than 65 years without significant comorbidities.²⁶ Outcomes for CLL with del(11q) are better with chemoimmunotherapy containing an alkylating agent. Therefore, FR is not recommended for CLL with del(11q).



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HDMP + Rituximab

High-dose methylprednisolone (HDMP) + rituximab is included with a category 2B recommendation for all patients, regardless of patient's age and comorbidities.¹²⁶ 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 [IVIG] to patients with infections and hypogammaglobulinemia).

Ibrutinib + Rituximab or Obinutuzumab

The results of recent randomized phase III trials demonstrated that ibrutinib + rituximab is more effective than chemoimmunotherapy with BR (Alliance North American Intergroup Study)²⁷ and ibrutinib + obinutuzumab is more effective than chlorambucil + obinutuzumab (iLLUMINATE study)^{22,122} for untreated CLL without del(17p) or *TP53* mutation in patients 65 years or older and for patients less than 65 years with comorbidities. The E1912 study also showed that ibrutinib + rituximab was more effective than FCR for patients 70 years or less without del(17p)/*TP53* mutation, especially for those with unmutated *IGHV*.¹¹⁶

Ibrutinib + obinutuzumab was recently approved by the FDA for first-line therapy based on the results of the iLLUMINATE study.¹²²

However, the results of two randomized studies did not show a benefit for the addition of rituximab to ibrutinib.^{22,127} In the Alliance North American Intergroup Study (A041202), the estimated 2-year PFS rates were 88% and 87%, respectively, for ibrutinib + rituximab and ibrutinib monotherapy ($P = .49$).²² 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.¹²⁷

The majority of the panel members acknowledged that the addition of rituximab to ibrutinib has not yet demonstrated improvement in clinical outcomes compared to ibrutinib monotherapy in a randomized clinical trial and there are no randomized clinical trials that have compared ibrutinib and ibrutinib + obinutuzumab. In all of the above mentioned randomized clinical trials that have evaluated ibrutinib + rituximab or obinutuzumab, ibrutinib was given continuously until disease progression and obinutuzumab or rituximab was added to the combination arm only for the first six 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 + obinutuzumab (for frail patients with significant comorbidities and patients aged ≥ 65 y and younger patients with significant comorbidities) and ibrutinib + rituximab (for patients < 65 y without significant comorbidities) are included as a category 2B (other recommended regimens) recommendation.

Pentostatin, Cyclophosphamide, and Rituximab

Pentostatin, cyclophosphamide, and rituximab (PCR) regimen is included as an option with a category 3 recommendation for patients less than 65 years without significant comorbidities.¹²⁸⁻¹³⁰

Monotherapy with Rituximab, Obinutuzumab, or Chlorambucil

With multiple randomized studies showing a survival advantage for combination regimens containing chlorambucil or rituximab or obinutuzumab compared to monotherapy with either of these agents, the majority of the panel members acknowledged that monotherapy with any of these agents is not an effective first-line treatment even for frail patients with comorbid conditions. However, some panel members felt



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that given the favorable tolerability profile, monotherapy with rituximab or obinutuzumab or chlorambucil might be an appropriate treatment option for a small fraction of very frail patients or patients 65 years or older with substantial comorbidities or decreased performance status for whom more intensive regimens are not appropriate.

Obinutuzumab monotherapy is included with a category 2B recommendation and monotherapy with rituximab or chlorambucil is included with a category 3 recommendation for frail patients with significant comorbidities and for patients 65 years or older or younger patients with significant comorbidities.^{131,132,133}

Post First-line Maintenance Therapy

In patients receiving BTKi (ibrutinib or acalabrutinib), continuation of ibrutinib or acalabrutinib is recommended (until disease progression) for patients with responding disease. Observation (until indications for retreatment) is recommended for patients achieving response to first-line chemoimmunotherapy or targeted therapy with fixed-duration treatment (venetoclax + obinutuzumab).

Lenalidomide maintenance after first-line chemoimmunotherapy is included as an option under *Other Recommended Regimens* for CLL without del(17p)/TP53 mutation in high-risk patients (MRD $\geq 10^{-2}$ or $\geq 10^{-4}$ and $< 10^{-2}$ with unmutated *IGHV*) based on the results of the CLLM1 study.¹³⁴

Second-line or Subsequent Therapy

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

Preferred Regimens

Acalabrutinib, ibrutinib, and VenR are included with a category 1 recommendation, based on the results of the phase III randomized studies (ASCEND, RESONATE, and MURANO, respectively).^{79,81,135,136}

Acalabrutinib is also effective for the management of patients with ibrutinib intolerance.¹³⁷ In a cohort of 33 patients with ibrutinib intolerance, after a median follow-up of 19 months, the ORR (including PR with lymphocytosis) was 76% and the median PFS was not reached. The estimated 1-year and 2-year PFS rates were 83% and 75%, respectively.

Although the panel acknowledged that idelalisib + rituximab (IdR) and duvelisib are preferred treatment options based on the efficacy data (in terms of median PFS) from randomized phase III studies,¹³⁸⁻¹⁴¹ the panel consensus was to include IdR and duvelisib with a category 2A recommendation due to their toxicity profile (colitis, diarrhea, and increased risk of infections). IdR is an appropriate treatment option for relapsed/refractory CLL/SLL in 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 grade ≥ 3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).

Clinicians should be aware of the increased risk for infections in patients with relapsed/refractory CLL. Anti-infective prophylaxis for herpes simplex virus (HSV), pneumocystis jirovecii pneumonia (PJP), and cytomegalovirus (CMV) reactivation are recommended for patients on idelalisib. Due to infection-related toxicity and deaths seen with idelalisib in previously untreated CLL in phase III clinical trials, it should not be used as first-line therapy.



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Other Recommended Regimens

FCR and PCR are included as options for relapsed/refractory therapy in patients <65 years without significant comorbidities.¹⁴²⁻¹⁴⁴ Reduced-dose FCR or PCR should be used for frail patients with significant comorbidities and for patients ≥65 years or younger patients with significant comorbidities.

FC + ofatumumab is approved for the treatment of patients with relapsed CLL and is included as an option for relapsed/refractory therapy, for patients <65 years without significant comorbidities.¹⁴⁵

The following regimens are included as options for relapsed/refractory disease regardless of patient's age or comorbidities:

- Alemtuzumab ± rituximab¹⁴⁶⁻¹⁴⁹
- Bendamustine and rituximab ± idelalisib or ibrutinib^{150,151,152}
- HDMP + rituximab^{153,154}
- Idelalisib^{155,156}
- Lenalidomide ± rituximab¹⁵⁷⁻¹⁵⁹
- Obinutuzumab or ofatumumab^{160,161}
- Venetoclax¹⁶²⁻¹⁶⁵
- Zanubrutinib (in patients with intolerance or contraindications to other BTKi)^{166,167}

Alemtuzumab + rituximab results in a higher ORR than that observed with alemtuzumab monotherapy and there was no significant difference in response rates between patients with fludarabine sensitive and fludarabine refractory disease.¹⁴⁸ 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.^{146,149}

BR regimen also has demonstrated activity in the subgroup of patients with fludarabine refractory disease. The results of recent phase III trials

have shown that the addition of idelalisib or ibrutinib to BR significantly improves PFS in patients with relapsed or refractory CLL.^{151,152}

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.^{153,154}

Lenalidomide ± rituximab also has 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. Lenalidomide can be given as continuous or intermittent dosing for patients with CLL.¹⁵⁷ Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment.

Idelalisib monotherapy also had clinical activity in relapsed/refractory CLL and SLL.^{155,156} As noted earlier, clinicians should be aware of the increased risk for infections in patients with relapsed/refractory CLL and anti-infective prophylaxis are recommended for patients on idelalisib.

Ofatumumab monotherapy has demonstrated activity in patients with fludarabine-refractory CLL with bulky lymphadenopathy (>5 cm; BF-ref CLL) and was also effective and well tolerated in patients with FA-ref CLL and previous rituximab exposure.^{168,169}

Venetoclax monotherapy has also shown promising activity in patients with relapsed or refractory CLL after prior ibrutinib or idelalisib.¹⁶²⁻¹⁶⁵

Zanubrutinib has demonstrated activity in patients with relapsed/refractory CLL in preliminary clinical trials.^{166,167} In a phase I study of patients with relapsed/refractory B-cell malignancies, zanubrutinib resulted in an ORR



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of 95% (80% PR) in the cohort of 56 patients with relapsed/refractory CLL with a low incidence of toxicities including atrial fibrillation and major bleeding.¹⁶⁶ Zanubrutinib may be an appropriate treatment option for patients with intolerance or contraindications to other BTKi. See *Special Considerations for the Use of Small Molecule Inhibitors* in this discussion on MS-21. An ongoing phase III trial is comparing zanubrutinib and ibrutinib in patients with relapsed/refractory CLL.

Post Second-line Maintenance Therapy

Ofatumumab maintenance or lenalidomide maintenance (category 2B) is included as an option (*Other Recommended Regimens*) in patients who are in CR or PR after second-line chemoimmunotherapy based on the results of the phase III randomized trials (PROLONG trial and CONTINUUM trial).^{170,171}

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

First-line Therapy: Preferred Regimens

Acalabrutinib ± obinutuzumab

In the ELEVATE-TN phase III study (discussed above) that demonstrated the efficacy of acalabrutinib ± obinutuzumab in 535 patients with previously untreated CLL, del(17p) and TP53 mutations were present in 10% and 12% of patients, respectively in the acalabrutinib + obinutuzumab arm.¹¹⁴ In the acalabrutinib monotherapy arm, del(17p) and TP53 mutations were present in 9% and 11% of patients, respectively. The PFS benefit for acalabrutinib ± obinutuzumab was seen across all patient subgroups including those with del(17p) or TP53 mutation.

Based on the recent FDA approval and the results of the ELEVATE-TN study, the panel consensus was to include acalabrutinib ± obinutuzumab with a category 2A recommendation.

Ibrutinib

Enrollment in an appropriate clinical trial is recommended for patients with del(17p) CLL. In the absence of a clinical trial, ibrutinib is the preferred treatment option. In a phase II trial that included 35 treatment-naïve patients with del(17p)/TP53 mutation (median age 62 years), at a median follow-up of 24 months, ibrutinib resulted in objective responses in 32 of 33 evaluable patients (55% of patients had a PR and 42% of patients had a PR with lymphocytosis) and the estimated OS at 24 months was 84%.¹⁷² After a median follow-up of 57 months, the estimated 5-year PFS and OS were 74% and 85%, respectively.¹⁷³ The cumulative incidence of progression at 24 months was 9%. Grade ≥3 neutropenia, anemia, and thrombocytopenia were reported in 24%, 14%, and 10% of patients, respectively. Grade 3 pneumonia and rash were reported in 6% and 2% of patients, respectively.

Patients with del(17p) CLL were excluded from the RESONATE-2 but 12 patients treated with ibrutinib had TP53 mutation.¹¹⁵ In the final analysis of this study, after 6-year follow-up, the median PFS was not reached and the estimated 5-year PFS rates was 56% for this group of patients. However, comparison between ibrutinib and chlorambucil could not be made since only 3 patients in the chlorambucil group has TP53 mutation.

Venetoclax + Obinutuzumab

In the CLL14 study (discussed above) that demonstrated the efficacy of this combination in 432 patients with previously untreated CLL, del(17p) and TP53 mutations were present in 9% and 11% of patients, respectively.¹¹³ The undetectable-MRD rate in peripheral blood at 3 months after completion of treatment (71% vs. 7%) and 24-month PFS rate (74% vs. 33%; HR, 0.31) were significantly higher for venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab in patients with del(17p) or TP53 mutation.



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The panel consensus was to include venetoclax + obinutuzumab as a preferred regimen with a category 2A recommendation. Observation is recommended for patients with responding disease.

First-line Therapy: Other Recommended Regimens

The panel emphasizes that the efficacy of BTKi (ibrutinib or acalabrutinib) and venetoclax + obinutuzumab in del(17p) CLL exceeds that of the other recommended regimens and should be considered as the best choice in the absence of a contraindication to give this treatment.

Zanubrutinib has demonstrated safety and efficacy in patients with previously untreated del(17p) CLL. In the prospectively enrolled non-randomized cohort (109 patients) of the phase III SEQUOIA trial that is comparing zanubrutinib and BR in patients with previously untreated CLL, zanubrutinib resulted in an ORR was 95% (3% CR; 87% PR).¹⁷⁴ After a median follow-up of 18 months, the median PFS and OS were not reached. The estimated 18-month PFS rate and OS rates were 89% and 95%, respectively. Zanubrutinib also had a favorable toxicity profile with low incidence of treatment-related adverse events.¹⁷⁴ Atrial fibrillation, bleeding of any grade and hypertension were reported in 3%, 6% and 8% of patients. Zanubrutinib may be an appropriate first-line therapy option for del(17p) CLL in patients with contraindications to other BTKi. See *Special Considerations for the Use of Small Molecule Inhibitors* in this discussion on MS-21.

Based on these results the panel consensus was to include zanubrutinib as an option with category 2A recommendation for patients with contraindications to other BTKi.

The following regimens are included as options (when BTKi or venetoclax is not deemed appropriate).

- Alemtuzumab ± rituximab¹⁷⁵⁻¹⁷⁸

- HDMP + rituximab¹²⁶
- Obinutuzumab¹³¹

Second-line or subsequent Therapy: Preferred Regimens

Acalabrutinib

In the phase II study that evaluated acalabrutinib in relapsed/refractory CLL, acalabrutinib resulted in an ORR of 93% in patients with del(17p) and 90% in those with CK.¹⁷⁹ In the ASCEND trial, PFS benefit for acalabrutinib was seen across all patient subgroups including those with del(17p) or *TP53* mutation.¹³⁵

Based on the results of the ASCEND trial, the panel consensus was to change the recommendation of acalabrutinib from category 2A (other recommended regimen) to category 1 (preferred regimen).

Ibrutinib

Ibrutinib is included with a category 1 recommendation. The results of the RESONATE-17 phase II study confirmed the safety and efficacy of ibrutinib in 145 patients with relapsed or refractory del(17p) CLL.¹⁸⁰ At a median follow-up of 12 months, the ORR (as assessed by the IRC) was 83%. In an extended analysis with a median follow-up of 28 months, the investigator-assessed ORR and the 24-month PFS and OS rates were 83%, 63%, and 75%, respectively.¹⁸⁰ In the RESONATE study, del(17p) (32% and 33%, respectively) and *TP53* mutation (51% and 46%, respectively) were present in similar proportions of patients in the ibrutinib and ofatumumab arm. The final analysis of this study also showed that the presence of del(17p)/*TP53* mutation or CK was not associated with inferior PFS outcomes.¹³⁶ 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 vs. 57 months for those without del(17p) or *TP53* mutation. Similarly, the median PFS was 41 months for patients with CK compared to 45 months for those without CK.



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Venetoclax ± Rituximab

In the phase III randomized MURANO study that compared VenR and BR in patients with relapsed/refractory CLL, VenR was superior to BR in prolonging PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation.¹⁸¹ Del(17p) and *TP53* mutation were present in 27% and 25% of patients, respectively, in patients randomized to VenR and in 27% and 28% of patients, respectively, in patients randomized to BR.

In a phase II study of 158 patients with relapsed or refractory del(17p) CLL, at a median follow-up of 23 months, venetoclax monotherapy resulted in an ORR of 77% (20% CR and 57% PR).¹⁸² The estimated 24-month PFS and OS rates were 54% and 73%, respectively. The ORR and the estimated 24-month PFS and OS were 63%, 50%, and 55%, respectively, for patients who had received prior BCRi therapy. The ORR was also high (>70%) in all subgroups of patients with additional risk features [eg, fludarabine-refractory status, bulky disease, del(17p), *TP53* mutation]. Neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%) were the most commonly treatment-related adverse events.

Based on these results, VenR is included with a category 1 recommendation and venetoclax monotherapy is included with a category 2A recommendation.

Duvelisib

In the phase III randomized study (DUO) that evaluated duvelisib for relapsed/refractory CLL (n = 319), del(17p), and/or *TP53* mutation were present in 31 out of 160 patients randomized to duvelisib.¹³⁹ The PFS advantage with duvelisib was maintained across all subgroups of patients, including those with del(17p) or *TP53* mutation. In the subgroup of patients with del(17p), the median PFS was significantly extended for duvelisib compared to ofatumumab (17 months vs. 9 months). 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.¹⁴¹

Idelalisib + Rituximab

In the phase III randomized study, IdR significantly prolonged survival in patients with del(17p) or *TP53* mutations compared with those treated with rituximab + placebo.¹⁸³ The median OS was 29 months for patients treated with IdR compared to 15 months for those treated with rituximab + placebo. IdR is included as an option with a category 2A recommendation.

Second-line or Subsequent Therapy: Other Recommended Regimens

The regimens listed below are included as options for relapsed/refractory therapy based on the results from retrospective analyses or subgroup analyses from the prospective clinical trials that had included patients with del(17p) or *TP53* mutation.

- Alemtuzumab ± rituximab^{147,148}
- HDMP + rituximab¹⁸⁴
- Idelalisib¹⁵⁵
- Lenalidomide ± rituximab^{157,158}
- Ofatumumab¹⁸⁵
- Zanubrutinib in patients with intolerance or contraindications to other BTKi^{166,167,186}

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.

Management of Resistance to Small-Molecule Inhibitors

Acquired resistance to ibrutinib and acalabrutinib is predominantly mediated by *BTK* and *PLCG2* mutations.^{68,187} *BTK* and/or *PLCG2*



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mutations have been detected at an estimated median of 9 months before relapse in patients treated with ibrutinib and these mutations have also been detected in patients with progressive CLL during ibrutinib therapy up to 15 months before the manifestation of clinical progression.^{68,188} *BTK* C481 mutations have been detected in 69% patients at the time of relapse at an estimated median of 12 months before relapse in patients treated with acalabrutinib.¹⁸⁷ Long-term follow-up is needed to confirm if *BTK* C481 mutations will emerge in patients treated with zanubrutinib.¹⁶⁶

Testing for *BTK* mutations may be helpful to confirm resistance to ibrutinib, acalabrutinib or zanubrutinib. However, the reported variant allele frequencies (VAF) are variable with often low VAF associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance.^{68,188}

Venetoclax is effective for the management of relapsed/refractory CLL after prior treatment with BCRi (ibrutinib or idelalisib)¹⁶²⁻¹⁶⁵ although the results of a pooled analysis from 4 clinical trials showed that BCRi-refractory CLL was significantly associated with lower CR rate and shorter duration of response.¹⁸⁹ Results from other retrospective analyses suggest that the use of venetoclax is associated with higher ORR and improved PFS following failure of ibrutinib (compared to failure of idelalisib) and also in patients who had received only one BCRi (compared to those who had received >1 BCRi).^{190,191}

Acquisition of *BCL2* mutations (*BCL2* G101V and *BCL2* D103Y) have been implicated in the development of resistance to venetoclax.^{192,193} *BCL2* G101V mutation (low VAF) has been identified in patients with progressive CLL during venetoclax therapy up to 25 months before the manifestation of clinical progression.¹⁹² Limited available data suggest that subsequent BTKi therapy or retreatment with venetoclax-based regimens is effective in patients with relapsed CLL following treatment

with venetoclax whereas PI3Ki following venetoclax do not appear to result in durable remissions.¹⁹⁴⁻¹⁹⁸

Testing for *BTK* or *BCL2* mutations as screening for resistance to BTKi or venetoclax is not currently recommended. *BTK* mutation analysis should be considered if acalabrutinib or zanubrutinib use is planned for a patient with ibrutinib intolerance, since acalabrutinib and zanubrutinib are not effective for ibrutinib-refractory CLL with *BTK* C481S mutations.

Special Considerations for the Use of Small-Molecule Inhibitors

BTK Inhibitors

Atrial fibrillation (grade ≥3), major hemorrhage (defined as serious or grade ≥3 bleeding events or central nervous system hemorrhage of any grade) and hypertension (grade ≥3) have been reported in 5%, 11% and 8% of patients treated with ibrutinib as first-line therapy, respectively.¹¹⁵ Atrial fibrillation (any grade), major hemorrhage and hypertension (grade ≥3) were reported in 4%, 5% and 11% of patients previously treated CLL.¹³⁶ Hypertension (grade ≥3) has uncommonly been the basis for discontinuation and should be managed with anti-hypertensives as appropriate.¹³⁶ In addition, ventricular arrhythmias, congestive heart failure and peripheral neuropathy have also been reported in patients treated with ibrutinib.¹³⁶

In the ELEVATE-TN trial, atrial fibrillation, hypertension (grade ≥3), bleeding of any grade, infections (grade ≥3) and secondary malignancies were reported in 4%, 2%, 39%, 14% and 9% of patients treated with acalabrutinib monotherapy, respectively and in 3%, 3%, 43%, 21% and 11% of patients treated with acalabrutinib/obinutuzumab, respectively.¹¹⁴ In the ASCEND trial, atrial fibrillation, hypertension, and bleeding of any grade were reported in 5%, 3%, and 26% of patients treated with acalabrutinib, respectively.¹³⁵ Grade ≥3 atrial fibrillation, hypertension, and



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bleeding were observed in 1%, 3%, and 2% of patients, respectively. Headaches commonly observed with acalabrutinib early in the treatment course typically resolve after 1 to 2 months of treatment and generally can be managed with analgesics (eg, acetaminophen) and caffeine supplements.

The benefit and risk of ibrutinib or acalabrutinib should be evaluated in patients requiring anti-platelet or anticoagulant therapies. Concomitant administration of ibrutinib or acalabrutinib with warfarin should be avoided. Monitoring for signs of bleeding, atrial fibrillation and hypertension along with appropriate management is recommended for patients receiving ibrutinib or acalabrutinib. Switching to alternate therapy should be considered, especially in patients with atrial fibrillation or hypertension that is not medically controllable. Transition to alternate therapy should be done as soon as possible since progression may accelerate when ibrutinib or acalabrutinib is stopped. Treatment-free interval should be as short as possible.

Zanubrutinib has a more favorable toxicity profile due to its highly specific BTK inhibition and can be co-administered with gastric acid reducing agents (proton pump inhibitors [PPI], H₂-receptor antagonists) and anticoagulants including warfarin.^{166,167,186} The use of anticoagulants including warfarin was not restricted in clinical trials evaluating zanubrutinib and no clinically significant differences in zanubrutinib pharmacokinetics were observed when co-administered with gastric acid reducing agents.^{166,167} Patients requiring warfarin have been excluded from clinical trials evaluating acalabrutinib and ibrutinib. Coadministration of acalabrutinib with PPI should be avoided. Thus, zanubrutinib may be an appropriate alternate treatment option for patients with intolerance or contraindications to other BTKi.

Hepatitis B virus (HBV) reactivation and invasive fungal infections have been rarely reported in patients treated with ibrutinib.^{199,200} There currently are no sufficient data to recommend routine screening and prophylaxis.

PI3K Inhibitors

Hepatotoxicity (transaminase elevations), severe diarrhea or colitis, infections, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib or duvelisib. Hepatotoxicity is a major concern in younger patients treated with idelalisib as first-line therapy.²⁰¹ Close monitoring of transaminase levels is essential and concurrent administration of idelalisib or duvelisib with other hepatotoxic drugs should be avoided.

Idelalisib and duvelisib are also associated with increased risk of opportunistic infections and febrile neutropenia. The addition of anti-CD20 mAb or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia.¹⁵² Anti-infective prophylaxis for HSV, PJP, and CMV reactivation are recommended for patients receiving idelalisib or duvelisib.

BCL-2 Inhibitors

TLS was an important side effect of venetoclax therapy in early clinical trials. Initiation at lower dose (20 mg for one week) and gradual step-wise ramp-up over 5 weeks to target dose (400 mg daily) along with prophylaxis for TLS is recommended to mitigate the risk and frequency of TLS in patients receiving venetoclax.²⁰² Initiation and accelerated escalation of venetoclax (20–400 mg over 3 weeks) with close inpatient monitoring for TLS can be done to quickly regain disease control in a selected subgroup of patients with high tumor burden, rapid disease progression, or disease relapse after treatment with BCRi therapy.^{162,203,204} This accelerated schedule has been explored in a small number of hospitalized patients, who received intensive monitoring and TLS prophylaxis. Additionally, continued treatment with BTKi concurrent with initiation and escalation of



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venetoclax with discontinuation of BTKi after venetoclax dose escalation to 400 mg daily can be considered.^{162,203,204} Recommendations for TLS prophylaxis based on tumor burden are outlined in CSLL-G.

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.

Allogeneic Hematopoietic Cell Transplant

Long-term results from several prospective studies have shown 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.^{54,205-211}

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 relapse/refractory CLL after initial purine analogue-based therapy.²¹²

Indications for Allogeneic HCT

Allogeneic HCT can be considered for CLL/SLL refractory to small-molecule inhibitor therapy in patients without significant comorbidities. HCT-specific comorbidity index (HCT-CI) could be used for the assessment of comorbidities prior to HCT and to predict the risks of non-relapse mortality and the probabilities of survival after HCT.^{213,214}

For patients with CLL/SLL with del(17p) or *TP53* mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if CK (≥ 3 abnormalities) is present. However, available data suggest that CK (≥ 5 abnormalities) is associated with inferior OS and

EFS following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics.^{215,216}

Histologic Transformation and Progression

Histologic transformation (also known as Richter's transformation) to more aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma (HL) occurs in about 2% to 10% of patients during the course of their disease and treatment.²¹⁷⁻²¹⁹ Unlike CLL, clinical outcomes in patients with histologic transformation are exceedingly poor with a pattern of no to minimal responses to chemoimmunotherapy regimens and a median survival of 5 to 12 months from diagnosis, although the median survival was significantly better for patients who did not receive prior treatment for CLL (46 vs. 8 months; $P < .001$).²²⁰⁻²²²

The exact mechanism of Richter's transformation is not well understood; however, it has been associated with molecular characteristics of the patients' CLL and prior CLL-directed therapies. The following molecular characteristics have been associated with the risk of developing Richter's transformation and may be linked to the pathogenesis of the disease.²²³⁻²²⁹

- Unmutated *IGHV* status
- Stereotyped BCR subset 8 combined with VH4-39 usage
- Cytogenetic abnormalities detected by FISH such as del(17p) and CK (≥ 3 clonal chromosome abnormalities)
- Genetic abnormalities such as *NOTCH1* mutation, *C-MYC* activation, or inactivation of *TP53* or *CDKN2A/B*.

The incidence of Richter's transformation increases with the number of prior chemoimmunotherapy regimens, and the rate is higher in patients treated with a combination of purine nucleoside analogues and alkylating agents.²²⁹ Richter's transformation has also been reported following treatment with ibrutinib and venetoclax.²³⁰⁻²³² Unlike progressive CLL,



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Richter's transformation developing after treatment with ibrutinib lacked resistance to *BTK* and *PLCG2* mutations.²³¹ While the rate of Richter's transformation during venetoclax therapy was significantly higher among patients with heavily pretreated del(17p) CLL, it was less common among a broader group of patients with less heavily pretreated relapsed/refractory CLL.²³² Further study is needed to determine the exact risk profile and mechanism of Richter's transformation.

CLL with expanded proliferation centers (accelerated CLL) may be diagnosed when proliferation centers in CLL are expanded or fused together and show a high Ki-67 proliferative rate (>40%). Progression to CLL with increased prolymphocytes (CLL-PLL) may occur when there are increased prolymphocytes in the blood (>10%–<55%). Neither of these findings is considered as Richter's transformation, but rather as progression of CLL, associated with a more aggressive disease course.²³³

Diagnosis and Workup

The diagnosis of Richter's transformation should be confirmed by excisional lymph node biopsy (if lymph node is accessible). Core needle biopsy is acceptable, when excisional or incisional lymph node biopsy is not feasible.

The workup of patients with Richter's transformation or progression is similar to that of patients with CLL/SLL and should include history and physical exam with attention to node-bearing areas, including Waldeyer's ring, and the size of liver and spleen, whole-body PET/CT scan, or chest/abdomen/pelvis CT with contrast of diagnostic quality. PET/CT scans are recommended to identify the optimal site for nodal biopsy, and biopsies should be directed to lesions with highest FDG uptake on PET scans.²³⁴⁻²³⁶

A maximum standardized uptake value (SUVmax) greater than or equal to 10 on PET scan has been shown to be a valid marker to distinguish

Richter's transformation from CLL among patients mostly treated with chemotherapy or chemoimmunotherapy.²³⁷ However, PET SUVmax greater than or equal to 10 alone lacks both sensitivity and specificity to distinguish Richter's transformation from CLL in patients who develop Richter's transformation while on ibrutinib.^{238,239} Tissue biopsy is required for the definitive diagnosis of Richter's transformation. PET alone is insufficient.

Epstein-Barr virus (EBV) infection has been reported in 16% of patients with Richter's transformation and is associated with a poor outcome.²⁴⁰ EBV infection of CLL can produce Reed-Sternberg (RS)-like proliferations, and presence of morphologic RS cells in a CLL background should not be considered as Richter's transformation. However, RS-like cells in a background of CLL may progress to classical HL in some patients.²⁴¹ Biopsy specimen should be evaluated for EBV infection using latent membrane protein 1 (LMP1) staining or EBV-encoded RNA in situ hybridization (EBER-ISH).

DLBCL arising from CLL can either be clonally unrelated to CLL (78%) or clonally related to CLL (22%).^{228,242} Richter's transformation to clonally unrelated DLBCL is characterized by a significantly lower prevalence of *TP53* disruption and a significantly longer median survival than clonally related DLBCL (62 months vs. 14 months).²²⁸ The majority of patients with Richter's transformation to clonally related DLBCL carry unmutated *IGHV*.²⁴² Molecular analysis is useful to establish the clonal relationship between baseline CLL tumor cells and histologically transformed tumor cells. *IGHV* gene sequencing or clonal *IGHV* rearrangements can be used to establish the clonal relationship between CLL and histologically transformed tumor cells.^{228,242}



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Richter's Transformation to DLBCL

Richter's transformation to clonally unrelated DLBCL should be managed similar to *de novo* DLBCL as outlined in the NCCN Guidelines for B-Cell Lymphomas.

Enrollment in a clinical trial is the preferred initial treatment option for Richter's transformation to clonally related (or unknown clonal status) DLBCL. In the absence of a suitable clinical trial, chemoimmunotherapy regimens recommended for DLBCL can be used; however, these regimens typically result in poor responses.²²⁰

The regimens listed below are used at the NCCN Member Institutions based on published data (mostly from single-arm phase I/II studies; [Table 3](#)) are listed below.

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)²⁴³
- R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)²⁴⁴
- R-hyper-CVAD (rituximab, cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone alternating with methotrexate and cytarabine)^{245,246}
- OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab)^{247,248}

Elevated platelet counts, higher hemoglobin levels, lower beta-2-microglobulin levels, and lower LDH levels have been identified as independent predictors of higher response rates to chemoimmunotherapy.²²⁰ However, the use of these prognostic variables for selection of therapy for Richter's transformation has not yet been established.

Allogeneic HCT can be considered for patients with disease responding to initial chemoimmunotherapy.^{220,249,250} In a non-randomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic HCT after achieving a CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo allogeneic HCT, or who underwent allogeneic HCT for relapsed or refractory Richter's transformation (75% vs. 27% and 21%, respectively; $P = .019$).²²⁰ In a retrospective analysis that evaluated the outcome after autologous or allogeneic HCT in 59 patients with Richter's transformation, the 3-year estimated OS, relapse-free survival (RFS), and cumulative incidences of relapse and non-relapse mortality rates were 36%, 27%, 47%, and 26%, respectively, for allogeneic HCT and 59%, 45%, 43%, and 12%, respectively, for autologous HCT.²⁴⁹ In a multivariate analysis, chemotherapy-sensitive disease and reduced-intensity conditioning were found to be associated with superior RFS after allogeneic HCT. Autologous HCT may also be appropriate for patients with disease responding to initial therapy but who are not candidates for allogeneic HCT due to age, comorbidities, or lack of a suitable donor.²⁴⁹

There are no effective treatment options for patients with Richter's transformation refractory to chemoimmunotherapy. Clinical trial is the preferred treatment option if available. Preliminary data from ongoing clinical trials suggest that anti-programmed cell death protein 1 (PD-1) mAbs (nivolumab and pembrolizumab) have promising activity in patients with Richter's transformation.²⁵¹⁻²⁵³

In a phase I/II study that included 20 patients with Richter's transformation, nivolumab + ibrutinib resulted in an ORR of 65% and the median PFS was 4 months.²⁵² Diarrhea (33%), neutropenia (31%), and fatigue (26%) of any grade were the most common treatment-related adverse events. Neutropenia (28%) and anemia (23%) were the most common grade 3 or



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4 adverse events and the incidence of grade 3 or 4 anemia was 35% in patients with Richter's transformation. In another phase II study of 25 patients (16 patients with relapsed CLL and 9 patients with Richter's transformation to DLBCL), the use of pembrolizumab as a single agent resulted in an ORR of 44% in patients with Richter's transformation and the median PFS and OS were 5 months and 11 months, respectively.²⁵³ Thrombocytopenia (20%), anemia (20%), neutropenia (20%), and dyspnea and hypoxia (8% each) were the most common grade 3 or 4 adverse events.

The panel acknowledged that there are limited published data supporting the use of nivolumab and pembrolizumab in patients with Richter's transformation refractory to chemoimmunotherapy or in patients with a del(17p)/*TP53* mutation and that additional data will be forthcoming. However, some panel members felt that given the unmet clinical need and the lack of effective treatment options, inclusion of PD-1 mAbs (nivolumab and pembrolizumab) as a treatment option is reasonable (based on the data discussed above) for patients with Richter's transformation refractory to chemoimmunotherapy (especially if considering allogeneic HCT). In addition, some panel members pointed out that these agents would also be appropriate as an initial treatment option for patients with del(17p) or *TP53* mutation and for those who are unable to receive chemoimmunotherapy regimens. Few panel members felt that monotherapy with PD-1 mAbs (nivolumab or pembrolizumab) is not an effective treatment option for patients with relapsed or refractory Richter's transformation outside of a clinical trial, citing a recent report in which the use of PD-1 mAbs for the treatment of relapsed/refractory Richter's transformation in a non-trial population (10 patients with biopsy-proven Richter's transformation to DLBCL and all patients had received prior therapy with BTKi) was associated with poor efficacy with a short time to treatment failure.²⁵⁴

Nivolumab and pembrolizumab ± ibrutinib are included as options with a category 2B recommendation for patients unable to receive chemoimmunotherapy, patients with del(17p) or *TP53* mutation, or those with chemoimmunotherapy-refractory disease.

Richter's Transformation to Hodgkin Lymphoma

Richter's transformation to HL is clinically less aggressive than Richter's transformation to DLBCL but it is associated with a poorer prognosis than de novo HL.^{218,219,255} Richter's transformation to HL should be managed as outlined in the NCCN Guidelines for Hodgkin Lymphoma. ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) was the most commonly used regimen resulting in an ORR of 68%, and achievement of CR to the ABVD regimen was the most important factor predicting survival of patients with Richter's transformation to HL.^{256,257}

CLL-PLL or Accelerated CLL

Clinical trial is the recommended treatment option since the optimal management is not established. In the absence of a suitable clinical trial, CLL-PLL should be managed with treatment options outlined for CLL/SLL based on the presence or absence of del(17p) or *TP53* mutation.

Supportive Care

Infections

Infectious complications are influenced by the progressive reduction in immunoglobulin levels (hypogammaglobulinemia) and are more common in patients with previously treated CLL.^{258,259} Patients with heavily pretreated fludarabine-refractory CLL have high susceptibility to developing serious infections.²⁶⁰

IVIg is associated with a significant decrease in the occurrence of infections but with no improvement in OS outcome.²⁶¹⁻²⁶⁵ Monitoring IVIg levels and monthly administration of IVIg (0.3–0.5 g/kg to maintain nadir



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levels of approximately 500 mg/dL) is recommended for selected patients with serum IVIG <500 mg/dL and recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.

Antiinfective prophylaxis is also appropriate for the management of patients who may be susceptible to certain infections due to a given treatment regimen. Antiinfective prophylaxis (herpes virus prophylaxis with acyclovir or equivalent), PJP prophylaxis with sulfamethoxazole trimethoprim, or equivalent is recommended for patients receiving purine-analog or bendamustine-based chemoimmunotherapy, idelalisib, corticosteroids, and/or alemtuzumab during treatment and thereafter.

Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients.²⁶⁶ All live vaccines should be avoided. Patients with CLL tend to have poor response to influenza vaccine and should be counseled to exercise care during influenza season even with vaccination. Protein and conjugate vaccines were shown to induce better responses than plain polysaccharide vaccines.^{267,268}

Hepatitis B Virus Reactivation

HBV reactivation has been reported in patients treated with chemotherapy ± immunotherapy agents.^{269,270} HBV carriers have a high risk of HBV reactivation. Fulminant hepatitis, hepatic failure, and death associated with HBV reactivation have occurred in patients receiving anti-CD20 mAb-containing regimens, including rituximab, obinutuzumab, or ofatumumab.²⁷¹ HBV reactivation has also been reported in patients treated with alemtuzumab, ibrutinib, and idelalisib. HBV prophylaxis and monitoring is recommended in high-risk patients receiving anti-CD20 mAb, alemtuzumab, purine analogs, ibrutinib, and idelalisib.

HBsAg and HBcAb testing is recommended for all patients receiving anti-CD20 mAb-based regimens. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be

obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. Patients receiving IVIG may be HBcAb positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.²⁷²

Prophylactic antiviral therapy with entecavir is recommended for patients who are HBsAg positive and undergoing anti-lymphoma therapy. Entecavir is more effective than lamivudine in preventing rituximab-associated HBV reactivation.^{273,274} Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes positive, consultation with a hepatologist and discontinuation of anti-CD20 mAb is recommended. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of treatment.²⁷⁵

Cytomegalovirus Reactivation

Clinicians should be aware of the high risk of CMV reactivation in patients receiving fludarabine-based chemoimmunotherapy, idelalisib, or alemtuzumab. Monitoring for the presence of CMV viremia using quantitative PCR (at least 2–3 weeks) is an effective approach to the management of CMV reactivation.²⁷⁶ Current practices for the management of CMV reactivation include the use of prophylactic ganciclovir if CMV viremia is present or the use of ganciclovir if the viral load is found to be increasing during therapy.^{277,278} Consultation with an infectious disease expert may be necessary.



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Autoimmune Cytopenias

Autoimmune hemolytic anemia (AIHA), immune-mediated thrombocytopenia (also known as immune thrombocytopenic purpura [ITP]), and PRCA are the most frequent autoimmune cytopenias in patients with CLL.^{279,280} Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias.

Although the direct antiglobulin test (DAT) was used for the diagnosis of AIHA, most patients with AIHA have a negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA.²⁸¹ Patients with advanced disease, unmutated *IGHV*, increased serum beta-2 microglobulin level, and high expression of ZAP-70 are also at a higher risk of developing AIHA.²⁸¹⁻²⁸⁴ Purine analog-based therapy was associated with AIHA. Recent studies

reported higher incidence of AIHA in patients treated with fludarabine or chlorambucil compared to those who received fludarabine-based combination regimens.^{281,285} AIHA should not preclude the use of combination therapy containing fludarabine. However, patients should be observed carefully and fludarabine therapy should be avoided in those where a history of fludarabine-associated AIHA is suspected.

ITP in patients with CLL is associated with poorer survival independent of common clinical prognostic variables.²⁸⁶ High white blood cell (WBC) count, unmutated *IGHV*, positive DAT, and ZAP-70 positivity are associated with the development of ITP in patients with CLL.²⁸⁶

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine,²⁸⁷ and splenectomy should be used in steroid-refractory cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias.²⁸⁸⁻²⁹² Eltrombopag and romiplostim are FDA-approved for the treatment of thrombocytopenia in patients with ITP that is refractory to steroids, IVIG, and splenectomy and have also been

shown to be effective for the management of CLL-associated ITP that is refractory to standard therapies.²⁹³⁻²⁹⁷

PRCA is less common in patients with CLL. PRCA can be managed with corticosteroids, cyclophosphamide, cyclosporine, or anti-thymocyte globulin.²⁸⁰ Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. In the very refractory cases, allogeneic HCT may be necessary. Evaluation of parvovirus B19 is also recommended for all patients with PRCA since patients with evidence of parvovirus B19 infection usually respond well to IVIG.²⁸⁰

Tumor Flare Reactions

Tumor flare reaction associated with lenalidomide is typically observed as painful enlargement of lymph nodes, and may be accompanied by lymphocytosis, spleen enlargement, low-grade fever, rash, and/or bone pain.⁷⁰ In patients with relapsed or refractory CLL, the 25 mg initial dose of lenalidomide used in patients with multiple myeloma resulted in excessive toxicity (tumor flare, tumor lysis, and myelosuppression).²⁹⁸ Initiation of lenalidomide at lower starting doses (5, 10, or 15 mg/day) and subsequent dose escalation by 5 mg up to a maximum of 25 mg/day is associated with an acceptable tolerability profile in patients with relapsed or refractory CLL (n = 103).²⁹⁹

The panel recommends the use of steroids to manage lymph node enlargement and inflammation, and antihistamines to manage rash/pruritus in patients who experience tumor flare reactions. Tumor flare prophylaxis with steroids may be considered for the first 10 to 14 days of therapy in patients with bulky lymph nodes (>5 cm). Severe tumor flare reaction is generally rare if an anti-CD20 mAb is initiated at least 1 week prior to the start of lenalidomide in patients treated with the combination regimen.



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Venous Thromboembolism

Lenalidomide may also be associated with venous thromboembolism (VTE) in patients with CLL/SLL.^{300,301} Prophylaxis with daily low-dose aspirin (81 mg daily) may be considered in patients with extremely high platelet counts at baseline. Patients already on anticoagulants, such as warfarin, do not need aspirin. However, it should be noted that these recommendations may differ from the NCCN Guidelines for Venous Thromboembolic Disease in which the recommendations for VTE associated with lenalidomide pertain only to patients with multiple myeloma.

Tumor Lysis Syndrome

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. TLS prophylaxis as noted in the *Supportive Care* section of the algorithm should be considered for these patients. TLS associated with venetoclax therapy should be managed as outlined in CSLL-G.

Management of Intolerance to anti-CD20 Monoclonal Antibody Therapy

Rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis can occur in patients treated with anti-CD20 mAb. Consultation with a dermatologist is recommended for management of these complications.

A rapid infusion over 90 minutes can be used if no severe infusion-related reactions were experienced with the prior cycle of rituximab. Re-challenge with the same anti-CD20 mAb is not recommended in patients experiencing aforementioned severe reactions to the chosen anti-CD20 mAb (rituximab, obinutuzumab, or ofatumumab). There are some data

(based on clinical experience) showing that substitution with an alternative anti-CD20 mAb is tolerated in patients experiencing severe reactions to a specific anti-CD20 mAb; however, it is unclear if such a substitution poses the same risk of recurrence.^{302,303}

Rituximab and hyaluronidase human injection for subcutaneous use is approved by the FDA for the treatment of patients with CLL based on the results of the SAWYER trial in which subcutaneous rituximab (rituximab with recombinant human hyaluronidase) had similar pharmacokinetic characteristics as IV rituximab when used in combination with fludarabine and cyclophosphamide.³⁰⁴ Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for intravenous rituximab in patients who have received at least one full dose of intravenous rituximab without experiencing severe adverse reactions.

Summary

The choice of first-line treatment for CLL/SLL should be based on the disease stage, presence or absence of del(17p) or *TP53* mutation, *IGHV* mutation status (if considering chemoimmunotherapy), patient's age, performance status, comorbid conditions, and the agent's toxicity profile.

Ibrutinib and acalabrutinib ± obinutuzumab are the preferred first-line therapy options for all patients including in high-risk subgroups such as those with del(11q) or del(17p)/*TP53* mutation and unmutated *IGHV*. Venetoclax + obinutuzumab is an effective fixed-duration chemotherapy-free first-line treatment option for all patients including those with del(17p)/*TP53* mutation. Idelalisib is not indicated in first-line treatment. FCR is preferred for patients less than 65 years with untreated *IGHV*-mutated CLL as it offers a defined treatment course and the majority of patients with *IGHV*-mutated CLL who receive first-line FCR are expected to have more than 10 years of PFS, and may potentially be cured of their disease.



Ibrutinib, idelalisib (\pm rituximab), acalabrutinib, duvelisib, and venetoclax \pm rituximab are effective treatment options for relapsed/refractory CLL/SLL. Zanubrutinib may be an appropriate treatment option for patients with contraindications or intolerance to other BTKi, including those with del (17p) CLL/SLL.

Histologic transformation of CLL to more aggressive lymphomas is associated with a poor prognosis. Precise diagnosis of histologic transformation and enrollment in clinical trials evaluating novel agents targeting the specific genetic abnormalities implicated in the pathogenesis of histologic transformation will improve the clinical outcomes of patients with histologic transformation.

Careful monitoring of adverse events after initiation of treatment and supportive care for the treatment-related complications should be an integral part of CLL/SLL management.



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Table 1: First-line Therapy for CLL Without del(17p)/TP53 Mutation

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
ELEVATE-TN ¹¹⁴	Acalabrutinib	179	≥65 years or <65 years with comorbidities (CIRS >6; CrCl <70 mL/min)	28 months	86% (1% CR)	Median: Not reached (2-year: 87%)	Median: Not reached (2-year: 95%)
	Acalabrutinib + obinutuzumab	179			94% (13% CR)	Median: Not reached (2-year: 93%)	Median: Not reached (2-year: 95%)
	Chlorambucil + obinutuzumab	177			79% (5% CR)	Median: 23 months (2-year: 47%)	Median: Not reached (2-year: 92%)
RESONATE-2 ¹¹⁵	Ibrutinib	136	≥65 years	5 years	92%	Median: Not reached (5-year: 70%)	Median: Not reached (5-year: 83%)
	Chlorambucil	133			37%	Median: 15 months (5-year: 12%)	Median: Not reached (5-year: 68%)
Alliance North American Intergroup Study (A041202) ²²	Ibrutinib	182	≥65 years	38 months	93%	2-year: 87%	2-year: 90%
	Ibrutinib + rituximab	182			94%	2-year: 88%	2-year: 94%
	Bendamustine + rituximab	183			81%	2-year: 74%	2-year: 95%
CLL14 study ^{77,113}	Venetoclax + obinutuzumab	216	≥65 years with comorbidities (CIRS >6; CrCl <70 mL/min)	40 months	85% (50% CR)	Median: Not reached 3-year: 82%	Median: Not reached 2-year: 92%
	Chlorambucil + obinutuzumab	216			71% (23% CR)	Median: 36 months 3-year: 50%	Median: Not reached 2-year: 93%
E1912 study ¹¹⁶	Ibrutinib + rituximab	354	≤70 years	34 months	96% (17% CR)	3-year: 89%	3-year: 99%
	FCR	175			81% (30% CR)	3-year: 73%	3-year: 92%
iLLUMINATE study ¹²²	Ibrutinib + obinutuzumab	113	≥65 years or <65 years with comorbidities (CIRS >6; CrCl <70 mL/min)	31 months	88%	Median: Not reached (30-month: 79%)	Median: Not reached (30-month: 86%)
	Chlorambucil + obinutuzumab	116			73%	Median: 19 months (30-month: 31%)	Median: Not reached (30-month: 85%)
CLL8 study ¹⁴	FCR	408	Median age 61 years with no comorbidities (median CIRS 6 and CrCl ≥70 mL/min)	6 years	90% (44% CR)	Median: 57 months	Median: Not reached
	FC	409			80% (22% CR)	Median: 33 months	Median: 86 months
CLL10 study ^{16,117}	FCR	196	Median age 61–62 years with no comorbidities (median CIRS 6 and CrCl ≥70 mL/min)	58 months	95%	Median: 58 months	Median: Not reached (5-year: 80%)
	Bendamustine + rituximab	171			96%	Median: 42 months	Median: Not reached (5-year: 81%)
CLL11 study ¹²¹	Chlorambucil + obinutuzumab	238	Median age 73 years with comorbidities (median CIRS 8 and CrCl 62 mL/min)		77% (22% CR)	27 months	
	Chlorambucil + rituximab	233			65% (7% CR)	16 months	
	Chlorambucil	118			31% PR	11 months	



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Table 2. Second-line and Subsequent Therapy for Relapsed/Refractory CLL Without del(17p)/TP53 Mutation

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
ASCEND trial ¹³⁵	Acalabrutinib	155	Median age 67–68 years with ECOG PS of ≤2 and adequate hematologic, hepatic, and renal function	16 months	81%	Median: Not reached (1-year: 88%)	N/A
	Idelalisib + rituximab	119			75%	Median: 16 months (1-year: 68%)	N/A
	Bendamustine + rituximab	36				Median: 17 months (1-year: 69%)	N/A
RESONATE ¹³⁶	Ibrutinib	195	Median age 67 years	65 months	91% (11% CR)	Median: 44 months	Median: 68 months
	Ofatumumab	196				Median: 8 months	Median: 65 months
MURANO ^{79,81}	Venetoclax + rituximab	194	≥18 years; ECOG PS 0–1; relapsed/refractory disease requiring therapy and adequate bone marrow, liver, and kidney function.	4 years	92%	4-year: 57%	4-year: 85%
	Bendamustine + rituximab	195			72%	4-year: 5%	4-year: 67%
Phase II trial: CLL progressing on ibrutinib ¹⁶²	Venetoclax	91	ECOG PS of ≤2 and adequate bone marrow function and CrCl ≥50 mL/min	14 months	65% (9% CR)	Median: 25 months (1-year: 75%)	1-year: 91%
Phase II trial: Relapsed or refractory CLL after idelalisib ¹⁶³	Venetoclax	36	ECOG PS of ≤2 and adequate bone marrow function and CrCl ≥50 mL/min	14 months	67% (8% CR)	1-year: 79%	1-year: 94%
Phase III trial ¹⁸³	Idelalisib + rituximab	110	CIRS>6, renal insufficiency, and/or poor bone marrow reserve that precluded use of chemoimmunotherapy	18 months	84%	Median: 19 months	Median: 41 months (2-year: 70%)
	Placebo + rituximab	110			16%	Median: 6.5 months	Median: 35 months (2-year: 52%)
DUO ¹³⁹	Duvelisib	160	Median age 69 years	22 months	74%	Median: 13 months (1-year: 60%)	Median OS not evaluable; Estimated 1-year OS rate: 86% for both arms
	Ofatumumab	159			45%	Median: 10 months (1-year: 39%)	
HELIOS trial ¹⁵¹	Bendamustine + rituximab + ibrutinib	289	≥18 years; ECOG PS 0–1; measurable lymph node disease (>1.5 cm) and adequate liver and kidney function.	35 months	87% (38% CR)	Median: Not reached (3-year: 68%)	3-year: 82%
	Placebo + bendamustine + rituximab	289			66% (8% CR)	Median: 14 months (1-year: 14%)	3-year: 73%
Phase II trial ¹⁵²	Bendamustine + rituximab + idelalisib	207	Measurable lymphadenopathy; disease progression within <36 months since last prior therapy; KPS score ≥60; adequate bone marrow, liver, and kidney function.	14 months	70%	Median: 21 months	Median: Not reached
	Placebo + bendamustine + rituximab	209			45%	Median: 11 months	Median: 32 months



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Table 3: Chemoimmunotherapy for Richter's Transformation

Regimen	No. of Patients	Median Follow-up	ORR	Median PFS	OS
RCHOP²⁴³	15	69 months	67% (7% CR)	10 months	Median: 21 months
REPOCH²⁴⁴	46	39 months	39%	4 months	Median: 6 months
R-hyperCVAD²⁴⁶	30	8 months	43% (27% CR)		1-year OS rate: 28%
OFAR²⁴⁷	20	9 months	50%		6-month OS rate: 53%
Modified OFAR²⁴⁸	35	26 months	39% (7% CR)		Median: 7 months 2-year OS rate: 20%



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