National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Version 2.2025 — February 7, 2025

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Discussion

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

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

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

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

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

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

Danielle Brander, MD ‡
Duke Cancer Institute

Matthew Cortese, MD, MPH † ‡ Þ
Roswell Park Comprehensive
Cancer Center

***Larry Cripe, MD ‡**
Indiana University Melvin and Bren Simon
Comprehensive Cancer Center

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

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

Lindsey Fitzgerald, MD ‡ Þ
Huntsman Cancer Institute
at the University of Utah

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

Sameh Gaballa, MD ‡
Moffitt Cancer Center

Muhammad Saad Hamid, MD †
St. Jude Children's Research Hospital/The
University of Tennessee Health Science Center

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

Paul Kaesberg, MD ‡ Þ
UC Davis Comprehensive Cancer Center

Brad Kahl, MD ‡
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Manali Kamdar, MD ‡
University of Colorado 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

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

Shazia Nakhoda, MD ‡
Fox Chase Cancer Center

***Sameer A. Parikh, MBBS ‡**
Mayo Clinic Comprehensive Cancer Center

Peter Riedell, MD ‡
The UChicago Medicine
Comprehensive Cancer Center

Andrew Schorr, MS ¥
Patient advocate

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

Madhav Seshadri, MD ‡
UCSF Helen Diller Family
Comprehensive Cancer Center

Tait Shanafelt, MD † ‡
Stanford Cancer Institute

Tanya Siddiqi, MD ‡
City of Hope National Medical Center

***Meghan Thompson, MD † ‡**
Memorial Sloan Kettering Cancer Center

***Chaitra Ujjani, MD ‡**
Fred Hutchinson Cancer Center

Riccardo Valdez, MD ≠
University of Michigan Rogel Cancer Center

Nina Wagner-Johnston, MD †
Johns Hopkins Kimmel Cancer Center

Jennifer A. Woyach, MD ‡
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

NCCN
Mary Dwyer, MS
Hema Sundar, PhD

ξ Bone marrow transplantation
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology/Hematopathology
¥ Patient advocacy
* Discussion Writing Committee Member

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NCCN Guidelines Version 2.2025
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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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.

Updates in Version 2.2025 of the NCCN Guidelines for CLL/SLL from Version 1.2025 include:

Global
- References updated throughout the guidelines.
- Venetoclax (ventoclax ± anti-CD20 mAb and ventoclax + ibrutinib) containing regimens are defined as BCL2 inhibitor (BCL2i)-containing regimens.
- Fixed duration treatment changed to Time-limited treatment
- Suggested treatment regimens separated by: BCL2i-containing regimens, cBTKi-based regimens, ncBTKi-based regimen, and PI3Ki-based regimens.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CSLL-4A
- CLL/SLL without del(17p)/TP53 mutation
  - First-line therapy, 1st option revised from "Covalent BTK inhibitor (cBTKi) ± obinutuzumab" to "Covalent BTK inhibitor (cBTKi)-based regimens."
  - Covalent BTK inhibitor (cBTKi)-based regimens (continuous treatment)
    - ◊ After intolerance, clarified as "Alternate cBTKi *or ncBTKi*".
    - ◊ After progression while on treatment, added: or ncBTKi.
  - BCL2 inhibitor (BCL2i)-containing regimens (Time-limited treatment)
    - ◊ Progression or intolerance while on treatment separated into "intolerance" and "progression while on treatment."
    - ◊ After progression while on treatment, clarified as "cBTKi or ncBTKi (if prior regimen included cBTKi)."

CSLL-4B
- CLL/SLL without del(17p)/TP53 mutation
  - Third-line therapy
    - ◊ After cBTKi, added: or ncBTKi.

CSLL-5
- CLL/SLL with del(17p)/TP53 mutation
  - BCL2 inhibitor (BCL2i)-containing regimens (Time-limited treatment)
    - ◊ After refractory or progressive disease, added: cBTKi or ncBTKi (if prior regimen included cBTKi)

CSLL-D 1 of 6
- First-line therapy, preferred regimens,
  - Added: Venetoclax+ acalabrutinib ± obinutuzumab (category 1)

CSLL-D 2 of 6
- Pirtobrutinib (resistance or intolerance to prior cBTKi-based regimens) moved from Useful in certain circumstances to Preferred regimens. (Also for CSLL-D 3 of 6)
- Therapy for relapsed or refractory disease, other recommended regimens, removed: Venetoclax + ibrutinib (category 2B). (Also for CSLL-D 3 of 6)

CSLL-D 3 of 6
- First-line therapy, preferred regimens,
  - Added: Venetoclax+ acalabrutinib ± obinutuzumab (category 2A)

CSLL-D 4 of 6
- Footnote q added: Venetoclax containing combinations with ibrutinib are not appropriate for patients who are intolerant to or have disease progression on ibrutinib.

Continued
UPDATES

Updates in Version 1.2025 of the NCCN Guidelines for CLL/SLL from Version 3.2024 include:

Global
- References updated throughout the guidelines.
- Covalent and noncovalent BTKi clarified throughout.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CSLL-1
- Diagnosis, Essential
  - 2nd bullet:
    - 1st sub-bullet revised: CLL diagnosis requires presence of monoclonal B lymphocytes ≥5 x 109/L in peripheral *blood based on flow cytometry*
    - 3rd sub-bullet revised: ...also include cytospin for cyclin D1 or fluorescence in situ hybridization (FISH) for t(11;14); t(11q;v) *to exclude mantle cell lymphoma (MCL)*.

CSLL-1A
- Footnotes removed: Cases diagnosed as B-cell prolymphocytic leukemia (B-PLL) are excluded from this guideline.

CSLL-3
- Branch point for Histologic transformation revised: Histologic transformation *(Richter)* ~~or Histologic progression of CLL/SLL~~

CSLL-4A
- CLL/SLL without del(17p)/TP53 mutation
  - First-line therapy, 1st option revised: *Covalent* BTK inhibitor (cBTKi) ± ~~anti-CD20 mAb~~ *obinutuzumab*
  - Treatment options for relapsed or refractory disease after prior therapy with cBTKi or ncBTKi- and venetoclax-based regimens (Also for CSLL-4B and CSLL-5) revised as:
    - Clinical trial ~~(preferred)~~ *or CAR T-cell Therapy (CSLL-D 3 of 6) or ncBTKi (if not previously given) (CSLL-D 3 of 6)* or Other Recommended Regimens (CSLL-D 3 of 6; Therapy for relapsed or refractory disease *after BTKi- and venetoclax-based regimens)...*
- Footnotes
  - Footnote u added: Patients who discontinue a cBTKi for intolerance can remain off treatment (if not progressive) for an extended period of time and alternate BTKi can be reinitiated when symptomatic. (Also for CSLL-4B)
  - Footnote v revised: In patients with no intolerance, ~~ibrutinib~~ *cBTKi* can be continued until disease progression while following recommended dose modification guidance as needed. (Also for CSLL-5)
  - Footnote w revised from, "Venetoclax + obinutuzumab preferred" to "Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission."
  - Footnotes removed: Elsawy M, et al. Br J Haematol 2015;170:574-583. (Also for CSLL-4B and 5)

CSLL-4B
- CLL/SLL without del(17p)/TP53 mutation
  - Third-line therapy
    - After second-line therapy with venetoclax ± anti-CD20 mAb, the option "or venetoclax ± anti-CD20 mAb" was added with footnote "w": Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.

CSLL-A
- Prognostic Variables In Patients With CLL/SLL table extensively revised.

Continued
UPDATES

Updates in Version 1.2025 of the NCCN Guidelines for CLL/SLL from Version 3.2024 include:

CSLL-C 3 of 5
- Cancer screening
  - 3rd bullet revised: ~~Standard~~ *Age appropriate* screening guidelines should be closely followed for breast, cervical, colon, and prostate cancers.
- Complications of mAb Therapy
  - 1st bullet added: Obinutuzumab infusion-related reactions (initial reaction and reactions in patients with high ALC [>100,000 µL]) can be severe and patients should be monitored closely. Consider premedication with corticosteroid, antihistamine, and acetaminophen. Monitoring and prophylaxis for TLS is recommended for patients with high ALC.

CSLL-C 5 of 5
- Vaccination changed to Immunizations
  - 1st bullet revised: Avoid all live vaccines *including live attenuated influenza vaccine*
  - 2nd bullet added: Recommended vaccinations
    - ◊ 4th sub-bullet added: Respiratory syncytial virus (RSV) vaccine: single dose vaccination for patients with CLL/SLL, including patients age <60 y
    - ◊ 5th sub-bullet revised: COVID-19 vaccine - sub-bullets related to vaccine and treatment removed. Sub-bullet added: See Management of Concurrent COVID-19 and Cancer in Patients in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections

CSLL-D 1 of 6
- CLL/SLL without del(17p)/TP53 mutation, First-line therapy
  - "Ibrutinib + obinutuzumab (category 2B)" and "ibrutinib + rituximab (category 2B)" moved from Other recommended regimens to Useful in certain circumstances and revised as "Ibrutinib + anti-CD20 mAb (category 2B)"
  - Other recommended regimens, Ibrutinib + venetoclax changed from a category 2B to category 2A

CSLL-D 2 of 6
- CLL/SLL without del(17p)/TP53 mutation
  - Second-line or ~~third-line~~ *subsequent* therapy
    - ◊ "Venetoclax + obinutuzumab" added to Preferred regimens
    - ◊ "Venetoclax + rituximab (category 1)" moved from Preferred regimens to Other recommended regimens
    - ◊ Useful in certain circumstances, For relapse after a period of remission *(*if previously used*)* - venetoclax ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) removed
    - ◊ Footnote ** added to venetoclax monotherapy: Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.
  - Therapy for Relapsed or Refractory Disease After Prior BTKi-and Venetoclax-Based Regimens
    - ◊ Following moved from Other recommended regimens to Preferred regimens
      - – Chimeric antigen receptor (CAR) T-cell therapy - Lisocabtagene maraleucel (CD19-directed)
      - – Pirtobrutinib (if not previously given)

Continued
UPDATES

Updates in Version 1.2025 of the NCCN Guidelines for CLL/SLL from Version 3.2024 include:

CSLL-D 3 of 6
- CLL/SLL with del(17p)/TP53 mutation
  - First-line therapy
    - ◊ Ibrutinib + venetoclax changed from a category 2B to category 2A
  - Second-line or ~~third-line~~ *subsequent* therapy
    - ◊ "Venetoclax + obinutuzumab" added to Preferred regimens.
    - ◊ "Venetoclax + rituximab (category 1)" moved from Preferred regimens to Other recommended regimens
    - ◊ Useful in certain circumstances, For relapse after a period of remission *(*if previously used*)* - venetoclax ± anti-CD20 mAb (venetoclax + obinutuzumab preferred) removed
    - ◊ Footnote ** added to venetoclax monotherapy: Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.
  - Therapy for Relapsed or Refractory Disease After Prior BTKi-and Venetoclax-Based Regimens
    - ◊ Following moved from Other recommended regimens to Preferred regimens
      - – Chimeric antigen receptor (CAR) T-cell therapy - Lisocabtagene maraleucel (CD19-directed)
      - – Pirtobrutinib (if not previously given)

CSLL-D 4 of 6
- Footnote g revised by adding: Awan F, et al. Blood Adv 2022;18:5516.

Histologic Transformation (Richter)
- Progression to CLL/PL or CLL with expanded proliferation centers pathway and associated footnotes removed.

HT-1
- Footnote c revised: ~~First, "CLL with expanded proliferation centers" or "accelerated CLL"~~ *Accelerated CLL or CLL with expanded proliferation centers* may be diagnosed in cases where proliferation centers in CLL are expanded or fused 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 prolymphocytes~~" (CLL/PL)~~ may occur when there are increased prolymphocytes in the blood (>10% to <55%) (>15%). Neither of these findings should be considered ~~a transformation event~~ *as Richter transformation*, but rather as progression of CLL *associated with more aggressive disease and poorer outcome (Gine E, et al. Haematologica 2010;95:1526-1533; Ciccone M, et al. Leukemia 2012;26:499-508; Campo E, et al. Blood 2022;140:1229-1253; Alaggio R, et al. Leukemia 2022;36:1720-1748). Optimal management for these cases has not been established.* ~~B-PLL should be reserved for the diagnosis of de novo leukemias that are not associated with CLL.~~

HT-3
- CIT-refractory or del(17p)/TP53 mutation
  - Additional therapy
    - ◊ CAR T-cell therapy - Lisocabtagene maraleucel (CD19-directed) added as a category 2A recommendation. Footnote j added.
  - Footnote i revised: Consider early referral for HCT *(Cwynarski K, et al. J Clin Oncol 2012;30:2211-2217) or CAR T-cell therapy for eligible patients.*

HT-A
- Suggested regimens if CIT is not preferred
  - Zanubrutinib + tislelizumab-jsgr added as a category 2A recommendation
  - Nivolumab ± ibrutinib changed from a category 2B to a category 2A recommendation
  - Pembrolizumab ± ibrutinib changed from a category 2B to a category 2A recommendation

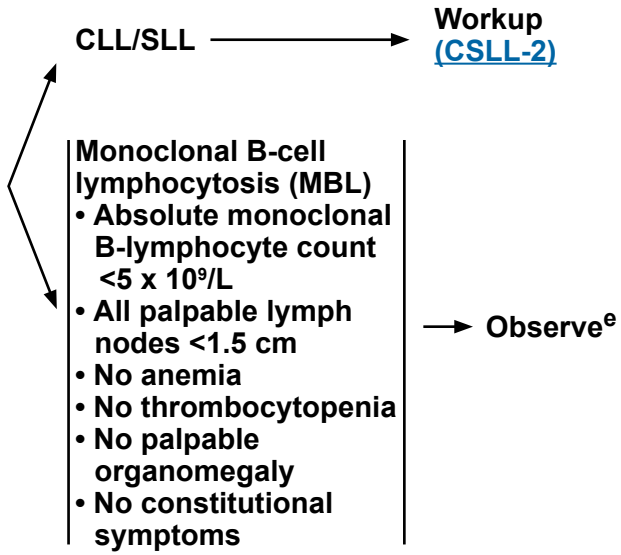
DIAGNOSIS

ESSENTIAL:

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

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 (CK)
- Molecular analysis to detect: Immunoglobulin heavy chain variable region gene (IGHV) mutation status
- Beta-2-microglobulin



Footnotes on CSLL-1A

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

FOOTNOTES

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

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

[c] LEF1 and SOX11 may be helpful in suspected cases of MCL that are cyclin D1-negative.

[d] Prognostic Variables for CLL/SLL (CSLL-A).

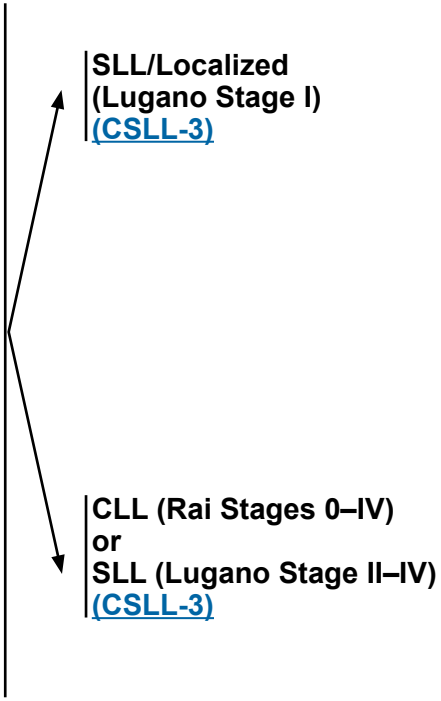
[e] Outside of clinical trials, CT scans are not required for diagnosis, serial monitoring, surveillance, routine monitoring of treatment response, or progression.

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

WORKUP

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

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **Quantitative immunoglobulins**
- **Reticulocyte count, haptoglobin, and direct antiglobulin test (Coombs)**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated[f]**
- **Uric acid**
- **Lactate dehydrogenase (LDH)**
- **Unilateral bone marrow aspirate and biopsy (may be informative for the diagnosis of immune-mediated or disease-related cytopenias)**
- **Hepatitis B[g] and C testing if treatment is contemplated**
- **Pregnancy testing in patients of childbearing age if systemic therapy or RT is planned**
- **Discussion of fertility preservation[h]**
- **FDG-PET/CT scan to direct nodal biopsy, if histologic transformation (Richter) is suspected. See HT-1.**

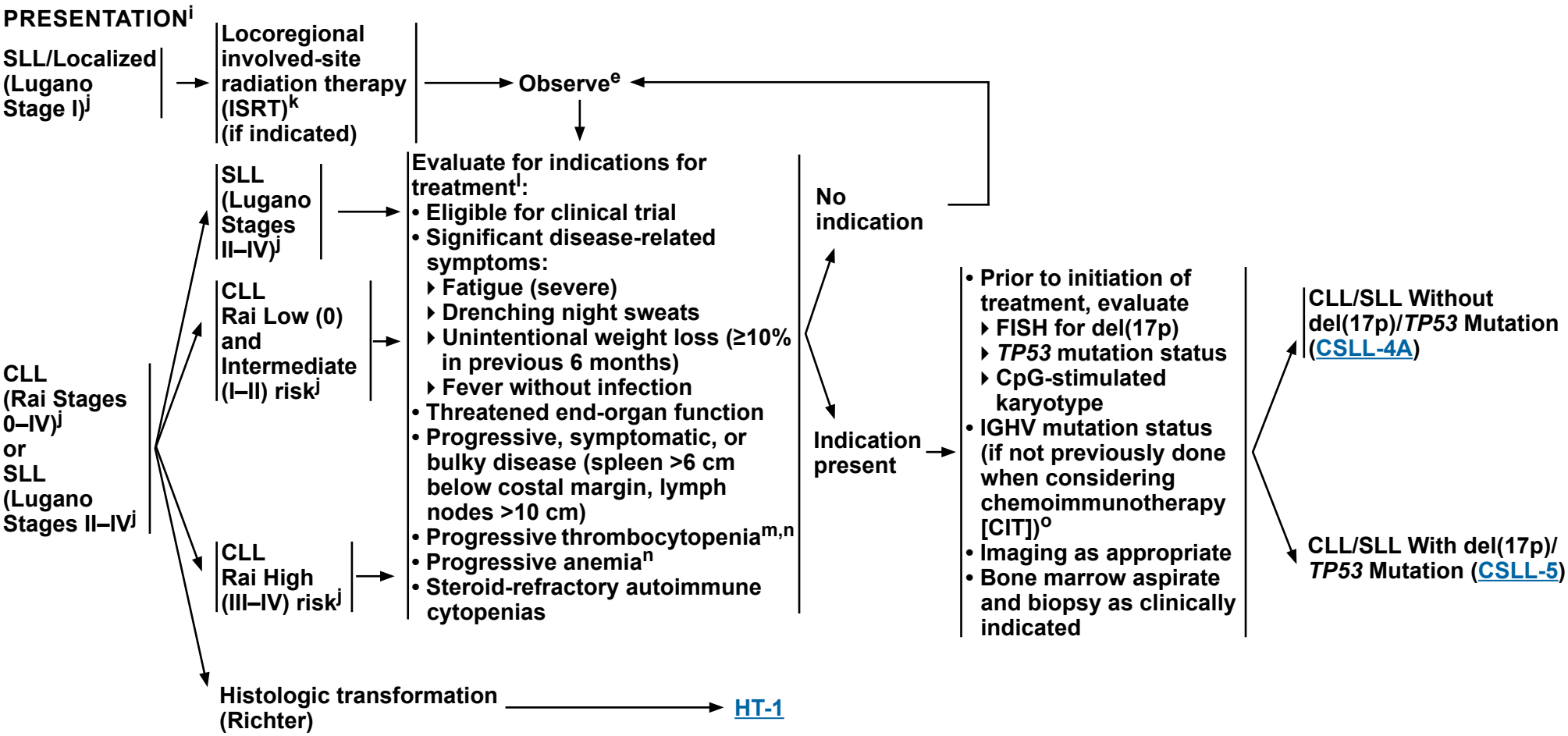


[f] Outside of clinical trials, CT scans are not required for diagnosis, serial monitoring, surveillance, routine monitoring of treatment response, or progression. CT scans may be warranted for the evaluation of symptoms of bulky disease or for the assessment of risk for TLS prior to initiating venetoclax.

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

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

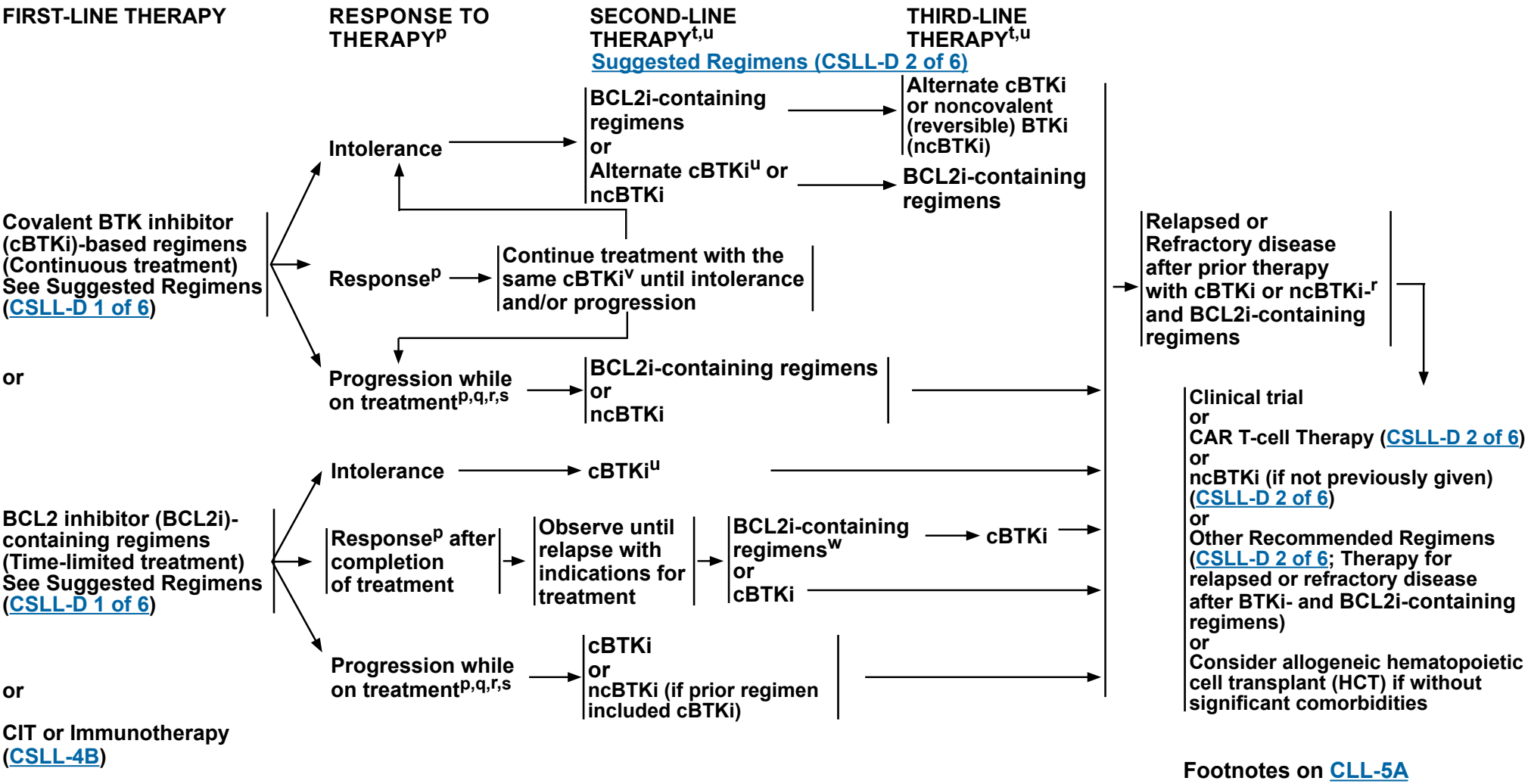
Note: All recommendations are category 2A unless otherwise indicated.



[e] Outside of clinical trials, CT scans are not required for diagnosis, serial monitoring, surveillance, routine monitoring of treatment response, or progression.
[i] 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] See NCCN Guidelines for B-Cell Lymphomas, Principles of Radiation Therapy for additional details.
[l] Absolute lymphocyte count (ALC) alone is not an indication for treatment in the absence of leukostasis, which is rarely seen in CLL.
[m] Platelet counts >100,000/μL 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 observed. Other causes of anemia/ thrombocytopenia (eg, autoimmune disorders, vitamin/iron deficiency) should be excluded.
[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.

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

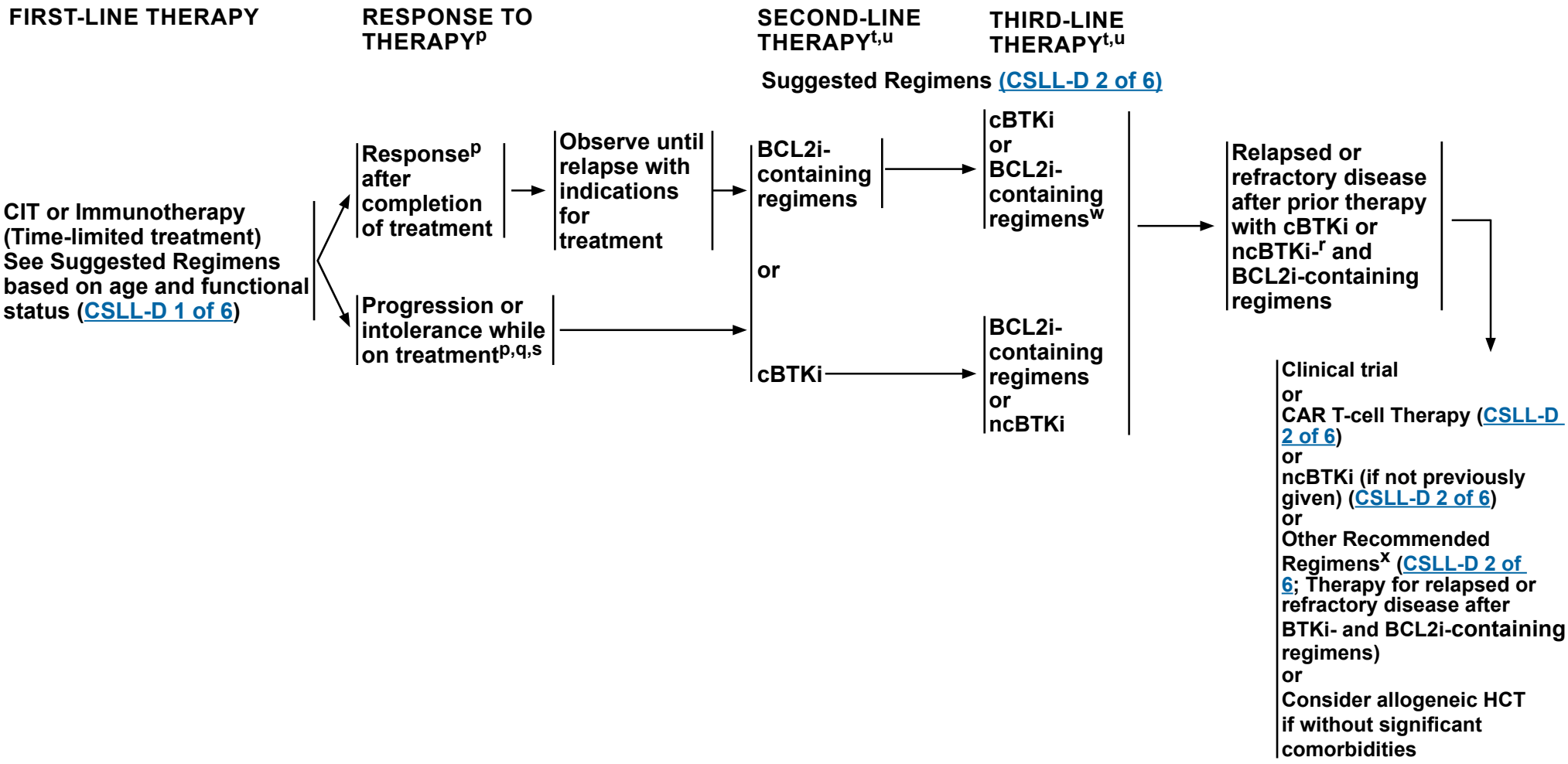
CLL/SLL WITHOUT DEL(17p)/*TP53* MUTATION[i]



Footnotes on CLL-5A

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

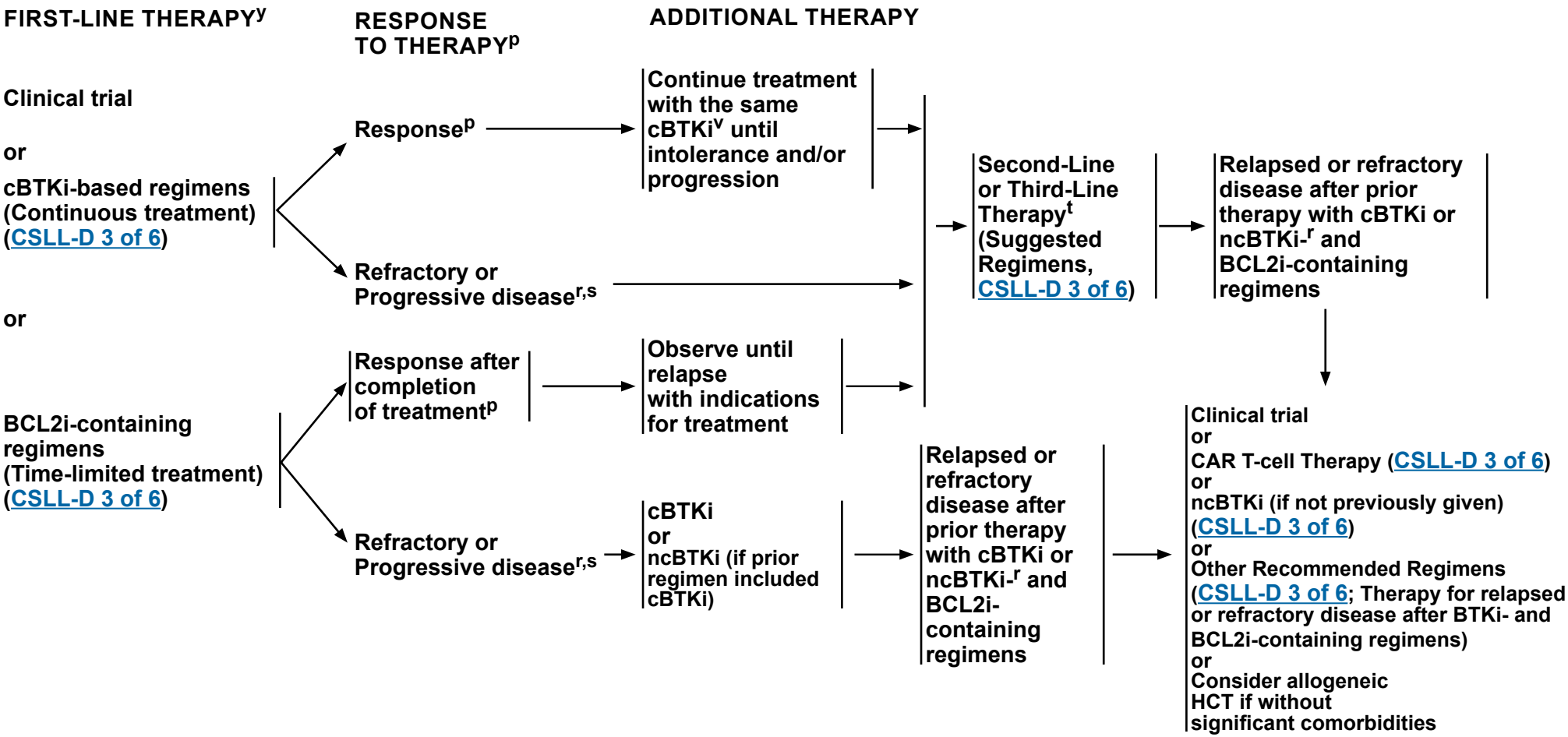
CLL/SLL WITHOUT DEL(17p)/*TP53* MUTATION[i]



Footnotes on CLL-5A

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

CLL/SLL WITH DEL(17p)/*TP53* MUTATION[i]



Footnotes on CLL-5A

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

FOOTNOTES FOR CSLL-4A, CSLL-4B, CSLL-5

[i] Supportive Care for Patients with CLL/SLL (CSLL-C).
[p] Response Definition After Treatment for CLL/SLL (CSLL-E).
[q] If progression with indication for subsequent therapy: Re-evaluate with FISH for del(17p)/TP53 mutation status and CpG-stimulated karyotype, prior to initiation of subsequent therapy.
[r] Testing for BTK and PLCG2 mutations may be useful in patients with disease progression or no response while on BTKi therapy including if poor adherence is considered as a possible cause. BTK and PLCG2 mutation status alone is not an indication to change treatment in absence of disease progression. Alternate cBTKi (acalabrutinib, ibrutinib, or zanubrutinib) could be considered for intolerance in absence of disease progression.
[s] Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation. If histologic transformation or histologic progression of CLL/SLL, see HT-1.
[t] In patients with disease responding to therapy: Continue the same BTKi until progression and/or intolerance. At time of disease progression, transition to next therapy as soon as possible. Treatment-free interval should be as short as possible. It is safe to overlap with venetoclax while on a BTKi. If treated with BCL2i-containing time-limited treatment, observe until relapse with indications for retreatment.
[u] Patients who discontinue a cBTKi for intolerance can remain off treatment (if not progressive) for an extended period of time and alternate BTKi can be reinitiated when symptomatic.
[v] In patients with no intolerance, cBTKi can be continued until disease progression while following recommended dose modification guidance as needed.
[w] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.
[x] CIT or immunotherapy is not an option for patients who have received these regimens for first-line therapy.
[y] CpG-stimulated karyotype is useful to identify patients with high-risk disease, particularly for patients receiving BTKi therapy.

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

PROGNOSTIC VARIABLES IN PATIENTS WITH CLL/SLL

Table 1: Cytogenetics and gene mutations

Method of Detection	Prognostic Variable	Clinical Association[a]
Interphase cytogenetics (FISH)	Del(13q) as a sole abnormality	Favorable prognosis: longest median overall survival (OS) in patients treated with chemoimmunotherapy (CIT).[1]
	Trisomy 12	Intermediate prognosis for time-to-first treatment (TTFT) in patients with newly diagnosed CLL; and intermediate OS in patients treated with chemoimmunotherapy.[1]
	None	Intermediate prognosis for TTFT in patients with newly diagnosed CLL; and intermediate OS in patients treated with chemoimmunotherapy.[1]
	Del(11q)	Shortened TTFT, and shorter median OS with chemoimmunotherapy.[1]
	Del(17p)[b]	• Inferior response, shorter treatment-free interval, and inferior survival with chemoimmunotherapy.[1-3] • Good responses but shorter progression-free survival (PFS) and OS with time-limited venetoclax-based regimens[4,5] and covalent BTK inhibitor (cBTKi).[6-10]
DNA sequencing	IGHV[c] Mutated: >2% mutation or <98% homology with germline gene sequence Unmutated: ≤2% of mutation or ≥98% homology with germline gene sequence)	• Unmutated IGHV is associated with shorter TTFT and PFS with chemoimmunotherapy and time-limited venetoclax-based regimens, compared to mutated IGHV.[3,5,11-15] • Overall response rates are not correlated with IGHV mutation status in patients treated with cBTKi or time-limited venetoclax-based regimens.[6-10] • PFS and OS are not correlated with IGHV mutation status in patients treated with cBTKi.[6,7,16]
	TP53 mutation[d] with del(17p)	• Shorter PFS and OS with chemoimmunotherapy,[e,17-21] time-limited venetoclax-based regimens[4,5] and cBTKi.[6-10] • Increased resistance to chemoimmunotherapy and targeted therapies; significantly shortened TTFT and time to next treatment (TTNT) and potentially increased risk for Richter transformation. • Low burden variant allele frequencies (VAF, <10%) may behave similar to wild type (WT).[22]
	TP53 mutation[d] without del(17p)	*TP53* mutation in the absence of del(17p) is associated with shortened PFS and OS However, PFS and OS outcomes on treatment with TP53 mutation but in absence of del(17p) may be more favorable than with concurrent *TP53* mutation and del(17p).[18,23]
	Other Significant Mutations	See Table 2 and Table 3 (CSLL-A 3 of 5)

See footnotes on CSLL-A (2 of 5)

See references on CSLL-A (4 of 5) and (5 of 5)

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

PROGNOSTIC VARIABLES IN PATIENTS WITH CLL/SLL

Table 1: Cytogenetics and gene mutations (continued)

Method of Detection	Prognostic Variable	Clinical Association[a]
CpG-stimulated metaphase karyotype[f]	Complex karyotype (CK) (≥3 unrelated clonal chromosome abnormalities in more than one cell on karyotype)	• Inferior survival and shorter time to disease progression with chemoimmunotherapy, time-limited venetoclax based regimens, and cBTKi.[24-27] • High CK (≥5 unrelated chromosomal abnormalities) is an adverse prognostic factor independent of clinical stage, IGHV mutation status, del(17p) and/or *TP53* mutation.[28,29]
Serum test	Beta-2 Microglobulin (B2M) (can be affected by renal dysfunction in a CLL-independent manner)	• Correlates with CLL/SLL disease burden and retains independent prognostic significance in multivariate models[30,31] • Elevated levels are associated with overall response, treatment free intervals, and OS in patients treated with frontline chemoimmunotherapy[32] • Reduction in levels associated with prolonged PFS in patients treated with ibrutinib[33,34]

See references on CSLL-A (4 of 5) and (5 of 5)

[a] This table provides the impact of molecular and cytogenetic variables on time-to-first treatment and survival for patients treated with chemoimmunotherapy and/or small molecule inhibitors. Prognostic markers and scoring systems (including CLL-IPI) can aid in integrating multiple variables, but OS can be underestimated for cohorts treated prior to the availability of current targeted/novel therapies.
[b] Prognostic significance may be dependent on the percentage of malignant cells with the deletion; prognosis is more favorable when the percentage of cells with del(17p) is low (Tam et al. Blood 2009;114:957-964; Van Dyke et al. Br J Haematol 2016;173:105-113). Patients with del(17p) often also have a concurrent *TP53* mutation.
[c] IGHV gene usage involving VH3-21 is considered higher risk regardless of the IGHV mutation status (Blood 2002;99:2262-2264; Blood 2002;100:1177-1184; Haematologica 2010;95:1705-1712). IGHV4–39 usage is associated with a higher risk for Richter's transformation (Rossi et al. Blood. 2007; 11: Abstract 3086).
[d] Patients can have *TP53* mutations independent of del(17p).*TP53* mutation status also provides additional prognostic information in addition to the cytogenetic abnormalities detected by FISH.
[e] Hazard ratios (HR) for PFS and OS with *TP53* mutation on treatment versus *TP53* WT are higher with chemoimmunotherapy compared to targeted therapies.
[f] Conventional metaphase FISH is difficult in CLL due to the very low in vitro proliferative activity of the leukemic cells. CK is based on results of metaphase karyotyping of CpG-stimulated CLL cells. Interphase FISH is the standard method to detect specific chromosomal abnormalities that may have prognostic significance. CpG oligonucleotide stimulation can be utilized to enhance metaphase cytogenetics.
[g] Cutoff values vary between institutions and studies. CLL-IPI utilizes a cutoff of >3.5 mg/L; other studies use a cutoff of 4 mg/L in patients treated with chemoimmunotherapy.

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

PROGNOSTIC VARIABLES IN PATIENTS WITH CLL/SLL

Table 2: Baseline and acquired gene mutations

Mutated Gene	Clinical Association
ATM[35-38]	• Shorter TTFT, PFS, TTNT and OS with CIT compared to WT
BIRC3[36,39,40]	• Shorter TTNT, PFS with CIT compared to WT • May be more sensitive to BCL2i-containing regimens
NOTCH1[4,36,41,42]	• Shorter TTFT and PFS irrespective of the IGHV mutation status and shorter TTNT with CIT compared to WT • Shorter OS in historical cohorts • Correlated with higher risk for Richter transformation
SF3B1[36,43]	• Shorter TTFT and OS with CIT compared to WT
TP53	• See Table 1 (CSLL-A 1 of 5)

Table 3: Gene mutations associated with resistance to targeted therapies

Mutated Gene	Clinical Association
BTK **(C481, L528 and T474)**[27,44-46]	• *BTK* C481 mutations have been detected in patients with disease progressing on cBTKi. • *BTK* L528 or T474 mutations have been detected in patients with disease progressing on cBTKi and noncovalent (reversible) BTKi (ncBTKi)
CARD11[47]	• Identified in patients with disease progressing on BTK inhibitors.
PLCG2[27,44-47]	
BCL2 **(G101V and D103Y)**[48,49]	• Identified in patients with disease progressing on venetoclax

See references on CSLL-A (4 of 5) and (5 of 5)

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

PROGNOSTIC VARIABLES IN PATIENTS WITH CLL/SLL
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Note: All recommendations are category 2A unless otherwise indicated.

PROGNOSTIC VARIABLES IN CLL/SLL
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Note: All recommendations are category 2A unless otherwise indicated.

CLL STAGING SYSTEMS

Rai System[a]

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood >5 x 10^9/L clonal B cells and/or >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 ≥100,000/mm^3 and <3 enlarged areas
B	Hemoglobin ≥10 g/dL and Platelets ≥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. © 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.

Continued

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

SLL STAGING SYSTEM

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

Stage[e]	Involvement[g]	Extranodal (E) Status
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	**Nodes on both sides of the diaphragm**	**Not applicable**
	Nodes above the diaphragm with spleen involvement	
Stage IV	**Additional non-contiguous extralymphatic involvement**	**Not applicable**

Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved. Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3068.

[d] Extent of disease is determined by FDG-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.

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

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Anti-infective Prophylaxis

- Recommended during treatment and thereafter (if tolerated) for patients receiving phosphoinositide 3-kinase (PI3K) inhibitors, purine analog- or bendamustine-based CIT, and/or alemtuzumab
  - Herpes virus prophylaxis with acyclovir or equivalent
  - Pneumocystis jiroveci pneumonia (PJP) prophylaxis with sulfamethoxazole/trimethoprim or equivalent
- Consider PJP and varicella zoster virus (VZV) prophylaxis in patients at increased risk for opportunistic infection and receiving BTKi therapy. Monitor for fungal infection.
- Monitor blood counts and consider fluoroquinolone and/or fungal prophylaxis for venetoclax-induced neutropenia.
- Hepatitis B virus (HBV) and cytomegalovirus (CMV) prophylaxis and monitoring is recommended for patients at high risk. See Treatment and Viral Reactivation below.

Viral Reactivation

HBV:

- Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) testing for all patients receiving therapy
  - Quantitative hepatitis B viral load by quantitative RT-PCR (qPCR) and surface antibody only if one of the screening tests is positive
- Patients receiving intravenous 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 (qPCR+), 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.[a] Avoid lamivudine due to risks of resistance development.
  - Other antivirals including adefovir, telbivudine, and tenofovir are proven active treatments and are acceptable alternatives.

Viral Reactivation (continued)

  - Monitor hepatitis B viral load with qPCR monthly through treatment and every 3 months thereafter.
    - ◊ If viral load is consistently undetectable, treatment is considered prophylactic.
    - ◊ If viral load does not drop or previously undetectable qPCR becomes positive, consult hepatologist.
  - Maintain prophylaxis up to 12 months after oncologic treatment ends.
    - ◊ Consult with hepatologist for duration of therapy in patient with active HBV.

Hepatitis C virus (HCV):

- Evidence from large epidemiology studies, molecular biology research, and clinical observation supports an association of HCV and B-cell non-Hodgkin lymphoma (NHL). 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 patients with previous CMV infection (seropositive):

- 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 PCR 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 (PML) related to JC virus can be seen in patients receiving treatment.

[a] Huang YH, et al. J Clin Oncol 2013;31:2765-2772; Huang H, et al. JAMA 2014;312:2521-2530.

Continued

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

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 (CSLL-F), CIT, 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**
    - ◊ **Glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to use of rasburicase. Rasburicase is contraindicated in patients with a history consistent with G6PD. In these patients, rasburicase should be substituted with allopurinol.**
    - ◊ **Low-Risk Disease:**
      Allopurinol or febuxostat beginning 2–3 days prior to CIT and continued for 10–14 days
    - ◊ **Intermediate-Risk Disease (Stage I/II and LDH <2X ULN):**
      Allopurinol or febuxostat
      OR
      Rasburicase if renal dysfunction and uric acid, potassium, and/or phosphate >ULN
    - ◊ **High-Risk Disease (Stage III/IV and/or LDH ≥2 X ULN):**
      Rasburicase
  - **Rasburicase (Doses of 3–6 mg are usually effective.[b] One dose of rasburicase is frequently adequate. Re-dosing should be individualized) is indicated for patients with any of the following risk factors:**
    - ◊ **Urgent need to initiate therapy in a patient with bulky disease**
    - ◊ **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.**

[b] There are data to support that fixed-dose rasburicase is very effective in adult patients.

Continued

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

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Autoimmune Cytopenias
- Autoimmune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, and direct antiglobulin test (Coombs).
  - AIHA that develops in the 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, herpesviruses, and drug effects.
- Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP), or BTKi-based therapy for steroid-refractory or recurrent AIHA.

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
- Patients with CLL/SLL have a higher risk of developing secondary cancers, including melanoma and non-melanoma skin cancers.[c]
- Risk factors for skin cancers include inability to tan, fair skin that sunburns easily, and a history of intensive sun exposure at a young age. Annual dermatologic skin screening is recommended.
- Age appropriate screening guidelines should be closely followed for breast, cervical, colon, and prostate cancers.

Complications of mAb Therapy
- Obinutuzumab infusion-related reactions (initial reaction and reactions in patients with high ALC [>100,000 µL]) can be severe and patients should be monitored closely. Consider premedication with corticosteroid, antihistamine, and acetaminophen. Monitoring and prophylaxis for TLS is recommended for patients with high ALC.
- 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 mAb in such settings is not recommended. It is unclear if re-challenge with alternative anti-CD20 mAb poses the same risk of recurrence. An alternative anti-CD20 mAb could be used for patients with intolerance (including those experiencing severe hypersensitivity reactions requiring discontinuation of chosen anti-CD20 mAb).

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.

Continued

[c] Mehrany K, et al. Dermatol Surg 2005;31:38-42; Mehrany K, et al. Arch Dermatol 2004;140:985-988; Mehrany, K et al. J Am Acad Dermatol 2005;53:1067-1071.

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

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 IVIG 0.3–0.5 g/kg or may substitute a subcutaneous immunoglobulin (SCIG) product given weekly at appropriately adjusted equivalent doses
  - 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 x 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
- 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
- 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)

Bleeding and Hemorrhage Risk with BTKi
- Increased risk for bleeding and bruising with cBTKI and ncBTKi. Hold 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure.
- Consider the benefit-risk in patients requiring antiplatelet or anticoagulant therapies; concomitant use of ≥3 anti-platelet agents not recommended (eg, BTKi, aspirin or other anti-platelet agents, direct oral anticoagulants).
- Thrombocytopenia (platelets <100,000/µL) and increased risk for bleeding should also be taken into consideration.

Continued

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

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Immunizations

- **Avoid all live vaccines including live attenuated influenza vaccine**
- **Recommended vaccines**
  - **Annual influenza vaccine[d]**
  - **Pneumococcal vaccine: see CDC Guidelines for Pneumococcal Vaccination**
  - **Zoster vaccine recombinant, adjuvanted for all patients treated with BTKi**
  - **Respiratory syncytial virus (RSV) vaccine: single dose vaccination for patients with CLL/SLL, including patients age <60 y**
  - **COVID-19 vaccine for all patients with CLL/SLL. See CDC COVID-19 Vaccination Clinical & Professional Resources**
    - ◊ **See Management of Concurrent COVID-19 and Cancer in Patients in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections**

[d] 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.

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

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

FIRST-LINE THERAPY[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• BCL2i-containing regimens ▸ Venetoclax[f,h] + obinutuzumab (category 1) ▸ Venetoclax[f,h] + acalabrutinib ± obinutuzumab (category 1) • cBTKi-based regimens ▸ Acalabrutinib[f,g] ± obinutuzumab (category 1) ▸ Zanubrutinib[f,g] (category 1)	• BCL2i-containing regimen ▸ Venetoclax[f,h] + ibrutinib[f,g] • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)	• Consider for IGHV-mutated CLL in patients aged <65 y without significant comorbidities ▸ FCR (fludarabine, cyclophosphamide, rituximab)[j,k] • cBTKi-based regimen ▸ Ibrutinib[f,g] + anti-CD20 mAb (category 2B)[l] • Consider when cBTKi and BCL2i are not available or contraindicated or rapid disease debulking needed ▸ Bendamustine[m] + anti-CD20 mAb[l,n] ▸ Obinutuzumab ± chlorambucil[o] ▸ High-dose methylprednisolone (HDMP) + anti-CD20 mAb[l] (category 2B; category 3 for patients <65 y without significant comorbidities)

Footnotes on CSLL-D 4 of 6

Suggested Regimens for Second-Line and Third-Line Therapy for CLL/SLL without del(17p)/*TP53* Mutation (CSLL-D 2 of 6)

Therapy for Relapsed or Refractory Disease After Prior BTKi-Based and BCL2i-Containing Regimens for CLL/SLL Without del(17p)/*TP53* Mutation (CSLL-D 2 of 6)

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

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

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

SECOND-LINE OR SUBSEQUENT THERAPY[e]	
Preferred Regimens	**Other Recommended Regimens**
• BCL2i-containing regimen ▸ Venetoclax[f,h] + obinutuzumab • cBTKi-based regimens ▸ Acalabrutinib[f,g,p] (category 1) ▸ Zanubrutinib[f,g,p] (category 1) • ncBTKi-based regimen:[f] ▸ Pirtobrutinib (resistance or intolerance to prior cBTKi-based regimens)	• BCL2i-containing regimens ▸ Venetoclax[f,h] + rituximab (category 1) ▸ Venetoclax[f,h,*] ▸ Venetoclax[f,h] + ibrutinib[f,g,q] (category 2B) • cBTKi-based regimen ▸ Ibrutinib[f,g,i] (category 1)

[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi-BASED AND BCL2i-CONTAINING REGIMENS[e]	
Preferred Regimens	**Other Recommended Regimens**
• Chimeric antigen receptor (CAR) T-cell therapy ▸ Lisocabtagene maraleucel (CD19-directed)[r] • ncBTKi-based regimen:[f] ▸ Pirtobrutinib (if not previously given)	• PI3Ki-based regimens[f] ▸ Duvelisib ▸ Idelalisib[s] ± rituximab • FCR[k,t] • Lenalidomide[u] ± rituximab • Obinutuzumab • Bendamustine[m] + rituximab[n] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) • HDMP + anti-CD20 mAb[l] (category 2B)

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

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

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

FIRST-LINE THERAPY[e]

Preferred Regimens

- BCL2i-containing regimens
  - Venetoclax[f,h] + obinutuzumab
  - Venetoclax[f,h] + acalabrutinib ± obinutuzumab
- cBTKi-based regimens
  - Acalabrutinib[f,g] ± obinutuzumab
  - Zanubrutinib[f,g]

Other Recommended Regimens

- BCL2i-containing regimen
  - Venetoclax[f,h] + ibrutinib[f,g]
- cBTKi-based regimen
  - Ibrutinib[f,g,i]

Useful in Certain Circumstances

- Consider when cBTKi and BCL2i are not available or contraindicated or rapid disease debulking needed
  - HDMP + anti-CD20 mAb[l]
  - Obinutuzumab

SECOND-LINE OR SUBSEQUENT THERAPY[e]

Preferred Regimens

- BCL2i-containing regimen
  - Venetoclax[f,h,*] ± obinutuzumab
- cBTKi-based regimens
  - Acalabrutinib[f,g,p] (category 1)
  - Zanubrutinib[f,g,p] (category 1)
- ncBTKi-based regimen:
  - Pirtobrutinib (resistance or intolerance to prior cBTKi-based regimens)

Other Recommended Regimens

- BCL2i-containing regimens
  - Venetoclax[f,h] + rituximab (category 1)
  - Venetoclax[f,h] + ibrutinib[f,g,q] (category 2B)
- cBTKi-based regimen
  - Ibrutinib[f,g,i] (category 1)

[*] Venetoclax ± anti-CD20 mAb (obinutuzumab preferred) is a treatment option for relapse after a period of remission.

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

Preferred Regimens

- Chimeric antigen receptor (CAR) T-cell therapy
  - Lisocabtagene maraleucel (CD19-directed)[r]
- ncBTKi-based regimen:[f]
  - Pirtobrutinib (if not previously given)

Other Recommended Regimens

- PI3Ki-based regimens[f] (in alphabetical order by category)
  - Duvelisib
  - Idelalisib[s] ± rituximab
- Alemtuzumab[v] ± rituximab
- HDMP + anti-CD20 mAb[l]
- Lenalidomide[u] ± rituximab

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

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

SUGGESTED TREATMENT REGIMENS FOOTNOTES

[a] See references for regimens on CSLL-D 5 of 6 and CSLL-D 6 of 6.
[b] Supportive Care for Patients with CLL/SLL (CSLL-C).
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route.
[d] Re-challenge with the same mAb is not recommended in patients experiencing rare complications (eg, mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis). It is unclear whether re-challenge with alternative anti-CD20 mAbs poses the same risk of recurrence.
[e] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[f] Please refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[g] A baseline cardiovascular risk assessment should be considered prior to initiation of cBTKi. Awan F, et al. Blood Adv 2022;18:5516.
[h] Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-F).
[i] The panel consensus to list ibrutinib under "other recommended regimens" is based on the toxicity profile.
[j] Data from the CLL10 study confirmed the superiority of FCR over bendamustine + rituximab (BR) in younger patients. For patients >65 y, the outcome was similar for both regimens with less myelosuppression and infection for BR. FCR was associated with improved PFS (with a plateau in PFS beyond 10-year follow-up) in patients with mutated IGHV without del (17p)/*TP53* mutation (Thompson P, et al. Blood 2016;127:303-309).
[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] Anti-CD20 mAbs include: obinutuzumab or rituximab.
[m] For patients aged ≥65 y or patients aged <65 y with significant comorbidities (CrCl <70 mL/min) dose is 70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated.
[n] Not recommended for frail patients.
[o] Recommended only for patients aged ≥65 y or patients aged <65 y with significant comorbidities (creatinine clearance [CrCl] <70 mL/min).
[p] 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.
[q] Venetoclax containing combinations with ibrutinib are not appropriate for patients who are intolerant to or have disease progression on ibrutinib.
[r] Refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.fda.gov/media/145711/download. See also CAR T-Cell–Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities for the management of cytokine release syndrome (CRS) and neurologic toxicity management.
[s] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or NCI CTCAE grade ≥3 neutropenia or grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).
[t] Recommended only for patients aged <65 y without significant comorbidities.
[u] 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.
[v] 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).

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

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Continued

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

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

RESPONSE DEFINITIONS AFTER TREATMENT FOR CLL/SLL[a]

Parameter	CR	PR	PD[b]	SD
Group A Lymph nodes	None ≥1.5 cm in longest dimension	Decrease ≥50% from baseline[c]	Increase ≥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 ≥50% from baseline	Increase ≥50% from baseline or from response	Change of –49% to +49%
Constitutional symptoms	None	Any	Any	Any
Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline[b]	Change of –49% to +49%
Group B Platelet count	≥100,000/μL	≥100,000/μL or increase ≥50% over baseline	Decrease ≥50% over baseline secondary to CLL	Change of –49% to +49%
Hemoglobin	≥11 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥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 ≥50% on successive biopsies	No change in marrow infiltrate
Neutrophils without growth factors	≥1500/μL			

Group A criteria define the tumor load. Group B criteria define the function of the hematopoietic system (or marrow).
Complete remission (CR): All of the criteria have to be met.
Partial remission (PR): At least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve.
Progressive disease (PD): At least 1 of the criteria of group A or group B has to be met.
Stable disease (SD): All of the criteria have to be met; constitutional symptoms alone do not define PD.

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

Footnotes on CSLL-E 2 of 2

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

RESPONSE DEFINITIONS AFTER TREATMENT FOR CLL/SLL[a]

Minimal Residual Disease (MRD) Assessment:

- **Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of time-limited treatment is an important predictor of efficacy.[e,f,g,h,i]**
- **Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and six-color flow cytometry (MRD flow) are the two validated methods used for the detection of MRD at the level of 10^{-4} to 10^{-5}.[j,k] Next-generation sequencing (NGS)-based assays have been shown to be more sensitive, thus allowing for the detection of MRD at the level of 10^{-6}.[l,m,n]**
- **MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method.**

[a] Hallek M, Cheson B, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.
[b] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.
[c] Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
[d] Spleen size is considered normal if <13 cm. There is no firmly established international consensus on the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.
[e] Al-Sawaf O, Zhang C, Jin HY, et al. Transcriptomic profiles and 5-year results from the randomized CLL14 study of venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in chronic lymphocytic leukemia. Nat Commun 2023;14:2147.
[f] Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: Primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE Study. J Clin Oncol 2021;39:3853-3865.
[g] Munir T, Moreno C, Owen C, et al. Impact of minimal residual disease on progression-free survival outcomes after fixed-duration ibrutinib-venetoclax versus chlorambucil-obinutuzumab in the GLOW study. J Clin Oncol 2023;41:3689-3699.
[h] Seymour JF, Kipps TJ, Eichhorst BF, et al. Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab. Blood 2022;140:839-850.
[i] Thompson PA, Peterson CB, Strati P, et al. Serial minimal residual disease (MRD) monitoring during first-line FCR treatment for CLL may direct individualized therapeutic strategies. Leukemia 2018;32:2388-2398.
[j] Rawstron AC, Kreuzer KA, Soosapilla A, et al. Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. Cytometry B Clin Cytom 2018;94:121-128.
[k] Wierda WG, Rawstron A, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. Leukemia 2021;35:3059-3072.
[l] Rawstron AC, Fazi C, Agathangelidis A, et al. A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study. Leukemia 2016;30:929-936.
[m] Logan AC, Gao H, Wang C, et al. High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment. Proc Natl Acad Sci U S A 2011;108:21194-21199.
[n] Aw A, Kim HT, Fernandes SM, et al. Minimal residual disease detected by immunoglobulin sequencing predicts CLL relapse more effectively than flow cytometry. Leuk Lymphoma 2018;59:1986-1989.

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

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

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

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

[a] Prescribing information for venetoclax. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208573s027lbl.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.

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

DIAGNOSIS

ESSENTIAL:

- **Excisional biopsy, if lymph node is accessible. Biopsy the lesion with highest standardized uptake value (SUV) on PET scan.**
- **FNA biopsy 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 biopsy in conjunction with appropriate ancillary techniques for the differential diagnosis (ie, IHC, flow cytometry) may be sufficient for diagnosis.**
- **Hematopathology review of all slides with at least one paraffin block representative of the tumor. Bone marrow aspirate with biopsy can be pursued if lymph node biopsy 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 transformation to DLBCL.[a,b,c]**
  - **Classic 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]**
- **Molecular analysis to establish clonal relatedness between CLL and DLBCL cells[e]**

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **FISH to detect +12; del(11q); del(13q); del(17p)**
- **CpG-stimulated metaphase karyotype for CK**
- ***TP53* sequencing**

→ **Workup** (HT-2)

[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] Accelerated CLL or CLL with expanded proliferation centers may be diagnosed in cases where proliferation centers in CLL are expanded or fused together (>20x field or 0.95 mm^2) AND show Ki-67 proliferative rate >40% or >2.4 mitoses/proliferation center. Progression to CLL with increased prolymphocytes may occur when there are increased prolymphocytes in the blood (>15%). Neither of these findings should be considered as Richter transformation, but rather as progression of CLL associated with more aggressive disease and poorer outcome (Gine E, et al. Haematologica 2010;95:1526-1533; Ciccone M, et al. Leukemia 2012;26:499-508; Campo E, et al. Blood 2022;140:1229-1253; Alaggio R, et al. Leukemia 2022;36:1720-1748). Optimal management for these cases has not been established.
[d] If morphologic RS cells are identified but the background cells are still the B cells of CLL, an EBV stain such as Epstein-Barr virus-encoded RNA (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 transformation event.
[e] Immunoglobulin gene rearrangement studies of CLL and histologically transformed tissue may be performed to establish the clonal relationship.

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

WORKUP

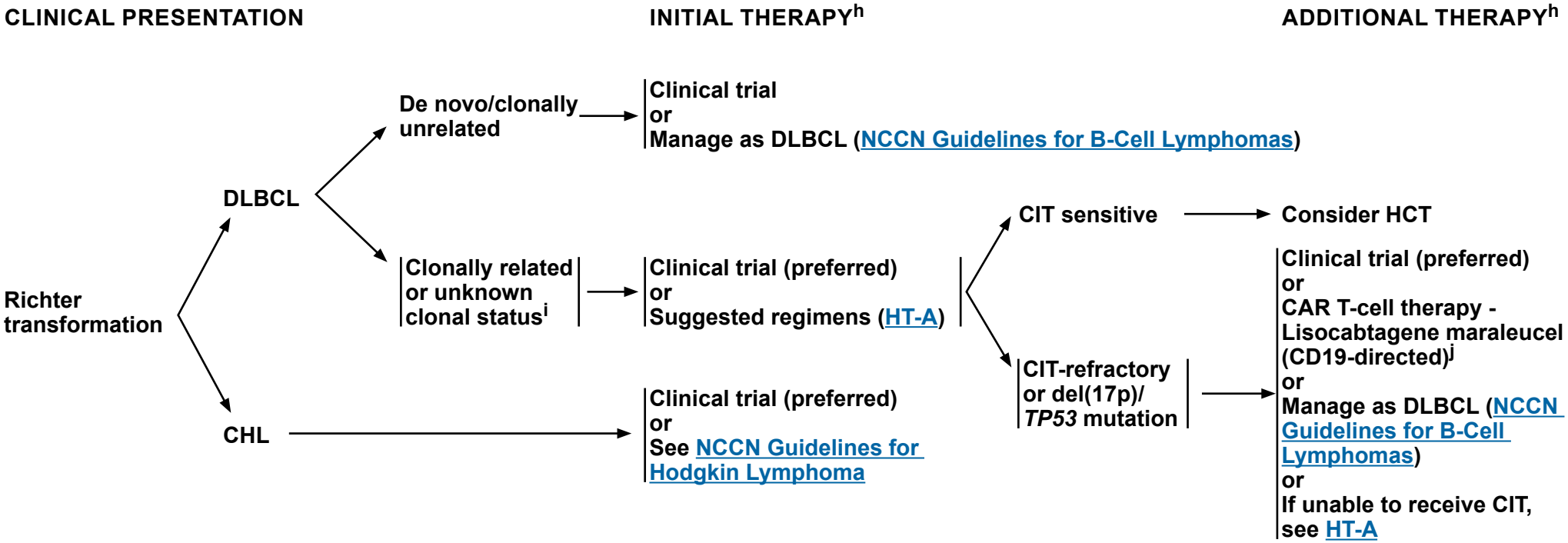
ESSENTIAL:
- **History and physical exam with attention to node-bearing areas, including Waldeyer's ring, and the size of liver and spleen**
- **Performance status**
- **B symptoms**
- **CBC with differential**
- **Comprehensive metabolic panel**
- **LDH, uric acid**
- **Whole body FDG-PET/CT scan or chest/abdominal/pelvic CT with contrast of diagnostic quality**
- **Molecular analysis to establish clonal relatedness between CLL and DLBCL cells[e]**

→ Richter transformation (HT-3)

USEFUL IN SELECTED CASES:
- **Unilateral bone marrow aspirate and biopsy**
- **Multigated acquisition (MUGA) scan/echocardiogram if anthracycline-based regimen is indicated**
- **Hepatitis B[f] and C testing**
- **Epstein-Barr virus (EBV) evaluation by EBV-latent membrane protein 1 (LMP1) or Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH)**
- **Pregnancy testing in patients of childbearing age**
- **Discussion of fertility preservation[g]**
- **Human leukocyte antigen (HLA) typing**

[e] Immunoglobulin gene rearrangement studies of CLL and histologically transformed tissue may be performed to establish the clonal relationship.
[f] Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, CIT, 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.
[g] Fertility preservation options include: sperm banking, semen cryopreservation, in IVF, or ovarian tissue or oocyte cryopreservation.

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



[h] Supportive Care for Patients with CLL/SLL (CSLL-C).
[i] Consider early referral for HCT (Cwynarski K, et al. J Clin Oncol 2012;30:2211-2217) or CAR T-cell therapy for eligible patients.
[j] Refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.fda.gov/media/145711/download. See also CAR T-Cell–Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities for the management of cytokine release syndrome (CRS) and neurologic toxicity management.

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

SUGGESTED TREATMENT REGIMENS[a]

RICHTER TRANSFORMATION TO DLBCL
(clonally related or unknown clonal status)

- **Suggested CIT regimens[b,c]**
  - **Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab)**
  - **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab**
  - **OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)**
  - **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)**
  - **Venetoclax[d,e] + RCHOP (category 2B)**

- **Suggested regimens if CIT not preferred (alphabetical order by category)[e]**
  - **Nivolumab ± ibrutinib[f]**
  - **Pembrolizumab ± ibrutinib[f]**
  - **Pirtobrutinib[**]**
  - **Zanubrutinib[*] + tislelizumab-jsgr**
  - **Acalabrutinib[*] (category 2B)**

[*] Covalent BTKi (cBTKi)
[**] Noncovalent (reversible) BTKi (ncBTKi)

[a] See references for regimens on HT-A 2 of 2.
[b] Richter 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 on HT-A are used at NCCN Member Institutions based on published data.
[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. An FDA-approved biosimilar is an appropriate substitute for rituximab.
[d] Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-F).
[e] Please refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[f] The panel acknowledged that there is a paucity of data for the use of these regimens in patients with Richter 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.

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

SUGGESTED TREATMENT REGIMENS – REFERENCES

Richter Transformation to DLBCL (clonally related or unknown clonal status)

Dose-adjusted-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, Khouri 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, 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 ± venetoclax

Tsimberidou AM, O'Brien S, Khouri 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.

Davids MS, Rogers KA, Jain N, et al. Initial results of a multicenter phase 2 study of venetoclax in combination with R-CHOP (VR-CHOP) for patients with Richter Syndrome [abstract]. Hematol Oncol 2023;41:466-468.

Davids MS, Rogers KA, Tyekucheva S, et al. Venetoclax plus dose-adjusted R-EPOCH for Richter syndrome. Blood 2022;139:686-689.

Acalabrutinib

Eyre TA, Schuh A, Wierda WG, et al. Acalabrutinib monotherapy for treatment of chronic lymphocytic leukaemia (ACE-CL-001): analysis of the Richter transformation cohort of an open-label, single-arm, phase 1-2 study. Lancet Haematol 2021;8:e912-e921.

Pirtobrutinib

Wierda WG, Shah NN, Cheah CY, et al. Pirtobrutinib, a highly selective, non-covalent (reversible) BTK inhibitor in patients with B-cell malignancies: analysis of the Richter transformation subgroup from the multicentre, open-label, phase 1/2 BRUIN study. Lancet Haematol 2024;11:e682-e692.

Nivolumab

Jain N, Senapati J, Thakral B, et al. A phase 2 study of nivolumab combined with ibrutinib in patients with diffuse large B-cell Richter transformation of CLL. Blood Adv 2023;7:1958-1966.

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

Armand P, Murawski N, Molin D, et al. Pembrolizumab in relapsed or refractory Richter syndrome. Br J Haematol 2020;190:e117-e120.

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.

Zanubrutinib + tislelizumab-jsgr

Al-Sawaf O, Ligtvoet R, Robrecht S, et al. Tislelizumab plus zanubrutinib for Richter transformation: the phase 2 RT1 trial. Nat Med 2024;30:240-248.

Lisocabtagene maraleucel

Winter AM, Bharadwaj S, Herrera AF, et al. Real-world outcomes of lisocabtagene maraleucel (liso-cel) in patients (pt) with Richter transformation (RT) from the Center for International Blood and Marrow Transplant Research (CIBMTR) [abstract]. J Clin Oncol. 2024;42:Abstract 7010.

Richter Transformation to Hodgkin Lymphoma

Stephens D, Boucher K, Kander E, et al. Hodgkin lymphoma arising in patients with chronic lymphocytic leukemia: outcomes from a large multi-center collaboration Haematologica 2021;106:2845-2852.

Parikh SA, Habermann TM, Chaffee KG, et al. Hodgkin transformation of chronic lymphocytic leukemia: Incidence, outcomes, and comparison to de novo Hodgkin lymphoma. Am J Hematol 2015;90:334-338.

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

ABBREVIATIONS

AIHA	autoimmune hemolytic anemia
ALC	absolute lymphocyte count
ANC	absolute neutrophil count
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
AST	aspartate aminotransferase
BTKi	BTK inhibitor PI3Ki
CAR	chimeric antigen receptor
CBC	complete blood count
cBTKi	covalent BTK inhibitor
CHL	classic Hodgkin lymphoma
CIT	chemoimmunotherapy
CK	complex karyotype
CMV	cytomegalovirus
CrCl	creatinine clearance
DAA	direct-acting antiviral
DLBCL	diffuse large B-cell lymphoma
EBER-ISH	Epstein-Barr virus-encoded RNA in situ hybridization
EBV	Epstein-Barr virus
ERIC	European Research Initiative on CLL
FISH	fluorescence in situ hybridization
FNA	fine-needle aspiration
G6PD	glucose-6-phosphate dehydrogenase
GVHD	graft-versus-host disease
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematopoietic cell transplant
HCV	hepatitis C virus
HLA	human leukocyte antigen
IHC	immunohistochemistry
ISRT	involved-site radiation therapy
ITP	immune thrombocytopenic purpura
IVF	in vitro fertilization
IVIG	intravenous immunoglobulin
LDH	lactate dehydrogenase
LMP1	latent membrane protein 1
mAb	monoclonal antibody
MBL	monoclonal B-cell lymphocytosis
MCL	mantle cell lymphoma
MRD	minimal residual disease
MUGA	multigated acquisition
ncBTKi	noncovalent BTK inhibitor
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PI3Ki	Pi3K inhibitor
PJP	pneumocystis jirovecii pneumonia
PML	progressive multifocal leukoencephalopathy
PRCA	pure red cell aplasia
qPCR	quantitative RT-PCR
RS	Reed-Sternberg
RT-PCR	reverse transcriptase polymerase chain reaction
SCIG	subcutaneous immunoglobulin
SUV	standardized uptake value
TLS	tumor lysis syndrome
ULN	upper limit of normal
VZV	varicella zoster virus
WBC	white blood cell

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

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred 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.

This discussion corresponds to the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Last updated: March 26, 2024.

Discussion

Overview

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are characterized by progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues.[1] Morphologically, these leukemic cells appear as small, mature lymphocytes that can be found admixed with occasional larger or atypical cells, or prolymphocytes. CLL remains the most prevalent adult leukemia in Western countries. In 2024, an estimated 20,700 people will be diagnosed with CLL in the United States, and an estimated 4440 people will die from the disease.[2]

CLL and SLL are essentially different manifestations of the same disease that are similarly managed.[1] The major difference is that in CLL, a significant number of the abnormal lymphocytes are found circulating in blood in addition to being resident in bone marrow and lymphoid tissue, while in SLL, the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues and there are few (if any) abnormal lymphocytes circulating in blood.

Guidelines Update Methodology

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

Literature Search Criteria

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 CLL and SLL 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: Randomized Controlled Trial; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial; Guideline; 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 were 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.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and

organizations to use more inclusive and accurate language in their future analyses.

Staging

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

The modified Rai classification stratifies patients into 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 historic median survival times of 150 months, 71 to 101 months, and 19 months, respectively, in the era of chemotherapy- and chemoimmunotherapy-based treatment.[4] Survival times in the current era of targeted therapy will most assuredly be improved and will become available with longer follow-up for patients who received targeted therapies.

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

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

Prognostic Factors

The prognostic significance of molecular and cytogenetic variables may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated. The impact of these variables on the clinical outcome are discussed below.

Immunoglobulin heavy chain variable region (IGHV) Gene Mutation

A cut-off level of 2% or less deviation from germline IGHV sequence is routinely used in clinical practice to differentiate patients with IGHV-unmutated CLL from those with IGHV-mutated CLL.[7-9] Percent deviation from the germline sequence was studied and higher levels were incrementally associated with favorable progression-free survival (PFS) and overall survival (OS) in patients treated with the FCR (fludarabine, cyclophosphamide, and rituximab), suggesting that IGHV mutation percentage is a continuous variable.[10]

IGHV gene mutation status correlated with time-to-first treatment (TTFT), response rates, PFS, and OS in patients treated with FCR.[11-13] In the CLL10 study, the PFS benefit of FCR was significant in physically fit patients <65 years and in patients with mutated IGHV.[12] Among patients with mutated IGHV gene, the median PFS was not reached with FCR compared to 55 months for bendamustine/rituximab (BR; $P = .089$). In a phase II study of 300 patients with previously untreated CLL, IGHV-mutated CLL (>2% mutation or <98% homology with germline gene sequence) was associated with long-term PFS, with a plateau on the PFS curve beyond 10 years following treatment with FCR (after a median follow-up of 19 years, the median PFS for patients with IGHV-mutated CLL was 15 years vs. 4 years for patients with IGHV-unmutated CLL).[13] In a multivariable analysis, IGHV-unmutated status and del(17p) were independently associated with significantly shorter PFS.

Unmutated IGHV (≤2% of mutation or ≥98% homology with germline gene sequence) is associated with unfavorable prognosis and significantly shorter survival compared to mutated IGHV in patients treated with chemoimmunotherapy-based regimens, independent of the stage of the disease.[14,15] 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).[16] Unmutated IGHV and/or

the VH3-21 gene usage was shown to be an independent predictor of shorter treatment-free interval and/or survival outcomes in patients treated with fixed-duration chemoimmunotherapy- and venetoclax-based regimens, even when high-risk genetic abnormalities were included in the multivariable regression models.[17,18] PFS and OS were not correlated with IGHV mutation status in patients treated with continuous BTK-inhibitor (BTKi)-based regimens.[19-21]

Continuous treatment with a covalent BTKi (ibrutinib, acalabrutinib, or zanubrutinib) results in high response rate and survival independent of the IGHV mutation status.[19,20,22-24] The ELEVATE-TN trial showed that acalabrutinib ± obinutuzumab resulted in greater PFS benefit compared to obinutuzumab + chlorambucil both in IGHV-unmutated and IGHV-mutated CLL; however, in patients with IGHV-mutated CLL, the PFS benefit was significant only for combined acalabrutinib + obinutuzumab.[20] In the ECOG-ACRIN cancer research group (E1912) study, ibrutinib + rituximab resulted in superior PFS compared to FCR in patients with IGHV-unmutated CLL (HR = 0.27; $P < .001$) and IGHV-mutated CLL (HR = 0.27; $P < .001$).[22] The biomarker subgroup analysis of the SEQUOIA study confirmed that PFS was significantly better for zanubrutinib (compared to BR) in patients with IGHV-unmutated and IGHV-mutated CLL.[23] In the FLAIR study, the PFS was significantly better for ibrutinib + rituximab (compared to FCR) in patients with IGHV-unmutated CLL; however, PFS was not significantly different between the treatment arms among patients with IGHV-mutated CLL.[24]

IGHV-unmutated status remains a prognostic factor for shorter PFS after fixed-duration treatment with venetoclax + obinutuzumab (VenO).[25-28] The extended follow-up data from the CLL14 study showed that VenO resulted in longer PFS for patients with IGHV-mutated CLL compared to those with IGHV-unmutated CLL (after a median follow-up of 52 months, the median PFS was not reached for patients in the IGHV-mutated group compared to 57 months for those in the IGHV-unmutated group).[25] In the phase III randomized GAIA-CLL13 trial, VenO with or without ibrutinib resulted in significant PFS benefit among patients with IGHV-unmutated CLL compared to IGHV-mutated CLL.[27] In the multivariable model, IGHV-unmutated status was an independent predictor of shorter PFS in the pooled VenO and VenO + ibrutinib arms.[28] Among patients with IGHV-unmutated CLL, the PFS was longer for patients randomized to VenO + ibrutinib compared to VenO.

Cytogenetic Abnormalities

Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) are present in more than 80% of patients with CLL.[29]

Del(13q) (55%), del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%) are the most common abnormalities at the time of diagnosis. Del(13q) as a sole abnormality was associated with favorable prognosis and the longest median survival (133 months) after chemoimmunotherapy. Del(11q) is often associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 months) after chemoimmunotherapy.

Del(17p) reflects the loss of the *TP53* gene and is frequently associated with mutation in the remaining *TP53* allele. Del(17p) is more frequently observed in patients with previously treated CLL [suggesting that acquisition and/or expansion of CLL clones with del(17p) may occur through treatment]. The prognostic significance of del(17p) may be dependent on the proportion of malignant cells with this abnormality, and the prognosis is more favorable when the percentage of cells with del(17p) is low.[30,31]

TP53 Aberrations

TP53 aberrations [del(17p) or *TP53* mutation] are predictors of poor outcomes with chemoimmunotherapy. Del(17p) is associated with poor response to chemoimmunotherapy, short treatment-free interval, and inferior survival.[13,29,32] *TP53* mutations are predictors of poor survival (independent of 17p chromosome status) to chemoimmunotherapy with fludarabine- or bendamustine-based regimens.[33-36]

TP53 aberrations also remain an independent predictor of inferior PFS and OS for fixed-duration treatment with venetoclax-based regimens.[26,37] Del(17p) and *TP53* mutation are independent predictors of PFS and OS whereas del(17p) and/or *TP53* mutation with IGHV-unmutated status is associated with the shortest PFS.[26,37] Continuous treatment with a covalent BTKi also results in shorter PFS and OS in patients with del(17p) or *TP53*-mutated CLL. The survival outcomes for CLL in patients with *TP53* aberrations treated with either a BTKi-based regimen or a venetoclax-based regimen are much better than the survival outcomes in patients treated with chemoimmunotherapy.

Recurrent Gene Mutations

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

An integrated prognostic model including *NOTCH1*, *SF3B1*, and *BIRC3* mutations along with the cytogenetic abnormalities detected by FISH was proposed to classify patients with newly diagnosed or previously untreated CLL who received rituximab-based chemoimmunotherapy or fludarabine or alkylating agent-based chemotherapy into 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].[43] The 10-year survival rates for the four subgroups were 29%, 37%, 57%, and 69%, respectively. This prognostic model may have limited utility since it excludes the IGHV mutation status.

Complex Karyotype

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

CK may be a stronger predictor of poor clinical outcomes than del(17p) or *TP53* mutation in patients with CLL treated with ibrutinib-based regimens.[45-48] It should be noted that in these studies, del(17p) often correlated with the presence of CK. Among patients with relapsed/refractory CLL treated with ibrutinib-based regimens, in a multivariable analysis, only CK was significantly associated with shorter event-free survival (EFS; $P = .006$), whereas CK ($P = .008$) and

fludarabine-refractory CLL (P = .005) were independently associated with shorter OS.[45] In an analysis of 308 patients treated with ibrutinib on four sequential clinical trials, in a multivariable analysis, CK at baseline, presence of del(17p), and age <65 years were all independently associated with shorter time to CLL progression.[48] In patients ≥65 years without CK or del(17p), the estimated cumulative incidence of CLL progression at 4 years was 2% compared to 44% in patients <65 years with CK and del(17p). CK was not associated with worse PFS in patients with treatment naïve CLL treated with zanubrutinib in the SEQUOIA study.[23]

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

Beta-2 Microglobulin

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

Prognostic Models

Several scoring systems and prognostic models incorporating traditional and newer prognostic markers were developed to more accurately predict the clinical course of disease and outcomes to treatment in patients with CLL/SLL.

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

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

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

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

The International Prognostic Score for Early-Stage CLL (IPS-E) predicts the likelihood of disease progression to need treatment in patients with early-stage CLL and stratifies patients with early-stage CLL into three risk groups with significantly different TTFT.[61] The cumulative risk for the need of treatment after 1 and 5 years of observation was 14% and 61%, respectively, for patients with high-risk IPS-E compared to 2% and 28% for patients with intermediate-risk IPS-E and <0.1% and 8% for patients with low-risk IPS-E. These findings need to be validated in a prospective clinical trial.

Targeted therapies with small molecule inhibitors have significantly improved survival outcomes and prognostic models were developed to predict the outcome of patients treated with targeted therapies.[54,55] The first prognostic model is predictive of survival in patients treated with ibrutinib and stratified patients into three risk groups (high [3–4 points]; intermediate [2 points]; and low [0 points]) based on *TP53* aberrations, prior treatment, elevated serum beta-2 microglobulin and LDH.[54] The 3-year PFS rates were 47%, 74%, and 87% for the high-, intermediate-, and low-risk groups, respectively ($P < .0001$). The corresponding 3-year OS rates were 63%, 83%, and 93%, respectively ($P < .0001$). This model remained significant in the stratification of patients with treatment-naïve and relapsed/refractory CLL. The second prognostic model identified patients with high-risk previously treated CLL who do not achieve a good outcome with available targeted therapies (ibrutinib, idelalisib, and venetoclax).[55] This prognostic model stratified patients into three risk groups based on elevated serum beta-2 microglobulin and LDH, hemoglobin, and time from initiation of last therapy (<24 months): low (score 0–1); intermediate (score 2–3); and high risk (score 4).

Response Criteria

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

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

Considering these findings, the iwCLL response criteria were revised to more precisely predict the outcome of patients with CLL treated with BTKi and PI3Ki.[64] The revised iwCLL response criteria allow for the response category, partial response (PR) with lymphocytosis (PR-L). In patients receiving BTKi (ibrutinib, acalabrutinib, zanubrutinib, or pirtobrutinib) or PI3Ki (idelalisib or duvelisib), this response category includes clinical

response (reduction in lymph nodes and splenomegaly with persistent lymphocytosis, in the absence of other indicators of progressive disease). Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

Minimal Residual Disease

Assessment of measurable residual disease (MRD; also referred to as minimal residual disease) is a highly sensitive indicator of disease burden in patients with CLL and MRD assessment as part of response evaluation is incorporated into some clinical trials. Consensus recommendations for the methodology for MRD determination, assay requirements and tissue selection (blood vs. bone marrow), and the use of MRD in clinical practice versus clinical trials were published.[65,66]

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

BTKi monotherapy does not typically result in uMRD but the use of covalent BTKi in combination with anti-CD20 monoclonal antibody (mAb) results in higher rates of uMRD compared to monotherapy.[20,73,74] In the E1912 phase III randomized trial that compared FCR vs ibrutinib + rituximab, among patients randomized to ibrutinib + rituximab there was no significant difference in PFS rates based on uMRD status.[75] PFS was significantly longer in patients with MRD levels of 10^{-1} and continuous treatment with ibrutinib was necessary to maintain treatment efficacy. The prognostic value of uMRD has not been confirmed in the context of BTKi monotherapy or in combination with anti-CD20 mAb.

uMRD4 at the end of treatment (EOT) with chemoimmunotherapy or venetoclax-based combination regimens is an independent predictor of improved survival among patients with previously untreated as well as relapsed/refractory CLL. Several randomized clinical trials showed that venetoclax-based combination regimens result in higher rates of undetectable MRD (uMRD; $<10^{-4}$, uMRD4 or $<10^{-6}$, uMRD6 in blood or bone marrow) than chemoimmunotherapy. uMRD4 rates at the EOT with venetoclax-based combination regimens from selected trials are summarized in Table 1.

The association between uMRD status at EOT and PFS are discussed below. However, it should be noted that none of the trials studied the use of MRD to direct treatment. MRD assessment may be useful in clinical practice to provide insight into anticipated PFS duration, but not to reliably recommend treatment duration or treatment decisions for patients on targeted therapy at the present time. At the present time, MRD assessment is not recommended (outside of clinical trials) as part of response evaluation.

Previously Untreated CLL/SLL

Chemoimmunotherapy

In the combined analysis of two randomized phase III studies (CLL8 and CLL10), MRD status at the EOT with chemoimmunotherapy correlated

with better survival in a multivariable analysis.[76] Among patients who achieved complete response (CR) and PR, PFS was longer for those with uMRD4 CR and uMRD4 PR (61 months and 54 months, respectively) than those with MRD-positive CR and MRD-positive PR (35 months and 21 months, respectively).[76] The persistence of post-treatment splenomegaly as a sole abnormality in patients with uMRD4 did not have a negative impact on PFS.

In a prospective study of 289 patients with previously untreated CLL, uMRD4 at the EOT with FCR correlated with longer PFS.[77] The median PFS was not reached for patients with uMRD compared to 38 months for those with detectable MRD ($P < .001$). MRD level (≤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 ≤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%.

Venetoclax + Obinutuzumab (with or without ibrutinib)

In the CLL14 study, uMRD4 status at the EOT correlated with improved survival in both treatment arms.[26] Deeper uMRD remissions (uMRD5 and uMRD6) were more frequent with VenO and PFS was longer in patients with uMRD6 compared to those with detectable MRD4 at EOT. The 4-year PFS rates were 77% for patients with uMRD6 and 36% for those with detectable MRD4. The 4-year OS rate was 89% for patients with uMRD4 and 64% for those with detectable MRD4.

In the phase III randomized GAIA–CLL13 trial, VenO (with or without ibrutinib) resulted in significantly higher uMRD4 rates ($P < .001$) compared to chemoimmunotherapy, but the uMRD4 rate was not significantly higher with venetoclax + rituximab (VenR; $P = .32$).[27] At 15 months after EOT, more patients achieved uMRD6 with VenO (60%) and VenO + ibrutinib (66%) than with chemoimmunotherapy (23%).[28] After a median follow-up of 51 months, uMRD6 was associated with longer PFS compared to detectable MRD6 in patients randomized to VenO with or without ibrutinib.[28]

Ibrutinib + Venetoclax

The results of the phase II randomized CAPTIVATE study showed that fixed-duration treatment with ibrutinib + venetoclax resulted in high rates of uMRD4 in all subgroups [del(17p) and/or mutated *TP53*, del(11q), and IGHV-unmutated CLL]. In the fixed-duration cohort, uMRD4 rates were 81% (blood) and 41% (bone marrow) for patients with del(17p) and/or mutated *TP53*; uMRD4 rates were higher in patients with IGHV-unmutated CLL (84% in blood; 64% in bone marrow) compared to IGHV-mutated CLL (67% in blood; 53% in bone marrow).[78] In the MRD cohort, patients were assigned to subsequent treatment based on the uMRD4 status at EOT.[79,80] Patients without confirmed uMRD4 were randomized to receive ibrutinib + venetoclax (n = 32) or ibrutinib (n = 31); post-randomization uMRD4 rates were higher with ibrutinib + venetoclax than with ibrutinib.[79] The estimated 3-year PFS rates were 97% for patients in both treatment arms. Patients with confirmed uMRD4 (n = 86) were randomized to receive placebo or ibrutinib. The estimated 4-year PFS rates were 95% for those assigned to ibrutinib and 88% for those assigned to placebo. The 4-year OS rates were not significantly different for the two treatment arms (100% and 98%, respectively).[80]

In the phase III randomized GLOW study, a higher rate of uMRD4 at 3 months after EOT (EOT+3) was observed with fixed-duration ibrutinib + venetoclax across all subgroups, including del(11q) and IGHV-unmutated CLL.[81,82] The estimated PFS rate for patients with uMRD4 in the bone marrow at 12 months after EOT (EOT+12) was 96% for ibrutinib + venetoclax compared to 83% for chlorambucil + obinutuzumab.[82] The rate of uMRD5 was also higher with ibrutinib + venetoclax (45% in blood; 40% in bone marrow) compared to chlorambucil + obinutuzumab (22% in blood and 6% in bone marrow). After a median follow-up of 55 months, PFS

benefit was observed, particularly in patients with IGHV-unmutated CLL, who achieved uMRD4 at EOT+3; PFS rates at 3 years after EOT were also higher with ibrutinib + venetoclax among patients with IGHV-mutated CLL independent of the MRD status at EOT+3.[83]

Treatment with ibrutinib + venetoclax for 2 years resulted in high uMRD4 rates in patients with previously untreated CLL/SLL.[84,85] In the interim analysis of the FLAIR study (274 patients randomized between ibrutinib and ibrutinib + venetoclax), the uMRD4 response rates were higher in patients with IGHV-unmutated CLL (83% in blood; 80% in bone marrow) compared to IGHV-mutated CLL (64% in blood; 56% in bone marrow) within 2 years of treatment with ibrutinib + venetoclax.[84] Large ongoing clinical trials will help to clarify the optimal duration of first-line treatment with combined targeted therapy and the importance of the difference in uMRD rates between IGHV-mutated and IGHV-unmutated CLL with different regimens.

Relapsed/Refractory CLL/SLL

In the MURANO study comparing VenR vs. BR, uMRD as best MRD response at any time during the study was higher with VenR (83% vs. 23%) and the 5-year follow-up data showed that uMRD at the EOT with VenR was associated with improved PFS and OS.[86,87] The 3-year PFS rates after EOT were 61% for those with uMRD4 compared to 41% for those with low-MRD-positive disease (10^{-4} to $<10^{-2}$). The 3-year OS rates after EOT were 95% and 73%, respectively, for those with uMRD4 and low-MRD-positive disease (10^{-4} to $<10^{-2}$) or high-MRD-positive disease ($>10^{-2}$).[87] Unmutated IGHV, del(17p), and genomic complexity (≥3 copy number variations) were associated with higher rates of conversion to detectable MRD4 and subsequent progressive disease after attaining uMRD4 at EOT.[87] Pre-existing *TP53*, *NOTCH1*, and *BIRC3* mutations were associated with lower rates of initial attainment of uMRD4 among patients treated with VenR.[88]

The results of the phase II single-arm CLARITY study showed that treatment with Ibrutinib + venetoclax also resulted in high rates of uMRD4 in patients with relapsed/refractory CLL/SLL.[89,90] The duration of treatment was based on the time to achieve uMRD4 in both blood and bone marrow (14 months for patients with uMRD4 at 8 months; 26 months for those with uMRD4 at 14 months and/or at 26-month follow-up; venetoclax was discontinued and ibrutinib was given until disease progression in patients with detectable MRD at 26 months). In an exploratory analysis, the achievement of uMRD4 after 6 months or a 2-log reduction in MRD levels after 2 months of treatment with ibrutinib + venetoclax resulted in sustained uMRD4 status and ability to discontinue treatment.[90]

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

Diagnosis

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

Immunophenotype by flow cytometry (blood) is adequate for the diagnosis of CLL; bone marrow biopsy is generally not required. A diagnosis of SLL should ideally be confirmed by lymph node biopsy. Evaluation of cyclin D1 (flow cytometry or IHC) or FISH analysis for t(11;14), flow cytometry evaluation of CD200, IHC for LEF1 and SOX11 may be helpful in the differential diagnosis of CLL, especially be helpful in suspected cases of mantle cell lymphoma that are cyclin D1-negative.[91-94]

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

Interphase FISH is the standard method to detect specific chromosomal abnormalities that may have prognostic significance. Conventional metaphase karyotype is difficult in CLL due to the very low *in vitro* proliferative activity of the leukemic cells. CpG oligonucleotide stimulation can be utilized to enhance metaphase cytogenetics.[95,96]

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

Monoclonal B-Cell Lymphocytosis

Monoclonal B-cell lymphocytosis (MBL) is a condition in which an abnormal monoclonal B-cell population with the immunophenotype of CLL is present but does not meet the diagnostic criteria for CLL.[97,98] An absolute monoclonal B-lymphocyte count of <5 x 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.[99]

MBL is further categorized into low-count MBL (<0.5 x 10^9/L) that rarely progresses to CLL and high-count MBL (0.5 – 4.9 x 10^9/L) that can progress to CLL requiring therapy at a rate of 1% to 2% per year.[100,101] High-count MBL is distinguished from Rai 0 CLL based on whether the monoclonal B-cell count is above or below 5 x 10^9/L.[102] A nodal variant characterized by nodal infiltration of CLL-line cells without apparent proliferation centers and absence of lymphadenopathy was also described in a subset of patients with MBL.[103]

MBL is associated with favorable molecular characteristics, including mutated IGHV and del(13q), lower prevalence of del(11q)/del(17p) and wildtype *TP53*, slower lymphocyte doubling time, longer treatment-free survival, and very low rate of progression to CLL.[98] Observation is recommended for all individuals with MBL.

Workup

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

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

CT scans are not generally recommended for routine monitoring of treatment response or disease progression in asymptomatic patients. CT scans may be useful for the evaluation of symptoms of bulky disease, or for the assessment of risk for tumor lysis syndrome (TLS) prior to the initiation of venetoclax and for treatment response assessment in patients with SLL. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.[104,105]

Assessment of Functional Status and Comorbidity

CLL/SLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. The age cutoff of 65 years is used in most of the chemoimmunotherapy-based clinical trials, including the studies conducted by the GCLLSG.[106] Comorbidities are frequently present in older patients and the presence of multiple comorbidities (≥2 comorbidities) was an independent predictor of clinical outcome, independent of patients' age or disease stage.[107]

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.[107,108] 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.[109,110]

First-Line Therapy

Localized SLL (Lugano stage I)

Locoregional radiation therapy (RT) 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 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 a randomized prospective phase III study of patients with early-stage high-risk CLL, although FCR resulted in high overall response rate (ORR) (93%) and significantly prolonged EFS (median not reached vs. 19 months; $P < .001$) compared 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).[111] The results of the CLL12 trial did not demonstrate survival benefit for early treatment with ibrutinib in patients with early-stage, high-risk CLL (high-risk defined according to the German CLL Study group index).[112]

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

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

In patients with indications for initiating treatment, age, functional status, comorbidities, and the presence or absence of del(17p) or *TP53* mutation should help to direct treatment options, as discussed below. Re-evaluation for *TP53* mutation status and del(17p) by FISH, and IGHV mutation status (if not previously done) are recommended prior to initiating treatment. IGHV mutation status is important for the selection of initial treatment when considering chemoimmunotherapy and is helpful in discussing the anticipated remission duration with fixed-duration targeted therapy. CpG-stimulated karyotyping is useful to identify patients with high-risk

CLL, particularly for treatment with targeted agents and developing a long-term treatment strategy.

In addition to the aforementioned disease- and patient-specific factors, agents' toxicity profile and duration of treatment (continuous vs. fixed duration) should also be considered for the selection of first-line therapy. Covalent BTKis (acalabrutinib, ibrutinib, and zanubrutinib) are given continuously until disease progression, whereas venetoclax-based combination regimens offer a fixed-duration treatment with a treatment-free remission period. As discussed earlier, fixed-duration treatment with venetoclax-based combination regimens also results in higher rates of uMRD, which is an independent predictor of improved survival.

The NCCN CLL Panel stratified all the regimens into 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 in certain circumstances.

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

Preferred Regimens

Covalent BTKi (acalabrutinib ± obinutuzumab, zanubrutinib) and VenO are included as preferred treatment options, based on the results of the phase III randomized studies (ELEVATE-TN, SEQUOIA, and CLL14).[20,21,110]

The efficacy data are discussed below and are summarized in Table 2.

Acalabrutinib ± Obinutuzumab

In the phase III ELEVATE-TN trial, acalabrutinib ± obinutuzumab resulted in superior PFS compared to chlorambucil + obinutuzumab in patients with previously untreated CLL.[20] Acalabrutinib + obinutuzumab was associated with a PFS benefit in patients with IGHV-unmutated CLL as well as IGHV-mutated CLL compared to chlorambucil + obinutuzumab. At a median follow-up of 75 months, 72-month PFS rate was longer with acalabrutinib + obinutuzumab compared to acalabrutinib (78% vs. 62%). There was also a trend towards improved OS for acalabrutinib + obinutuzumab (72-month OS rate was 84% compared to 76% for acalabrutinib monotherapy), although the study was not powered to compare the PFS benefit between the two acalabrutinib arms.[113]

Acalabrutinib was granted broad FDA approval for the treatment of patients with untreated and relapsed/refractory CLL based on the results of the ELEVATE-TN and ELEVATE-RR trials.[20,114] Acalabrutinib ± obinutuzumab is included with a category 1 recommendation.

Venetoclax + Obinutuzumab

The CLL14 study established VenO as an effective fixed-duration chemotherapy-free first-line treatment option with significantly improved PFS compared to chlorambucil + obinutuzumab in patients ≥65 years, or younger patients with comorbidities (CIRS score >6 or an estimated CrCl <70 mL/min).[109,110] The uMRD4 rate at the EOT was significantly higher with VenO (74% vs. 34%; $P < .0001$), and this combination was also associated with lower rate of conversion to MRD-positive status 1 year after treatment.[25]

VenO was granted broad FDA approval for the treatment of patients with CLL and is included with a category 1 recommendation for patients ≥65 years or younger patients with significant comorbidities.

The efficacy of VenO in patients <65 years of age without significant comorbidities was established in the phase III randomized GAIA–CLL13 trial.[27] The 4-year follow-up data confirmed that VenO with or without ibrutinib was associated with superior PFS compared to chemoimmunotherapy (FCR or BR).[28] The panel members agreed that VenO is also an appropriate fixed-duration chemotherapy-free treatment option for younger patients without comorbidities and the panel consensus

was to include VenO with a category 1 recommendation for patients <65 years of age without significant comorbidities.

Zanubrutinib

Zanubrutinib is a highly selective/specific covalent BTKi that is FDA-approved for the treatment of CLL. In the phase III SEQUOIA study, zanubrutinib resulted in higher ORR and statistically significant improvement in PFS compared to BR in patients with untreated CLL without del(17p)/*TP53* mutation (HR = 0.42; *P* < .0001).[21] The biomarker subgroup analysis from the SEQUOIA study confirmed that PFS benefit with zanubrutinib was observed in all subgroups including patients with del (11q) (*P* <.001), unmutated IGHV (*P* <.0001) and mutated IGHV (*P* < .01).[23]

Based on the results of the SEQUOIA study, zanubrutinib is included with a category 1 recommendation.

Other Recommended Regimens

Ibrutinib

In the RESONATE-2 study, after a median follow-up of 5 years, ibrutinib resulted in a significantly higher ORR (*P* < .0001) and significantly longer PFS rate (*P* < .0001) compared to chlorambucil in patients ≥65 years without del(17p).[115] 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. Extended long-term data confirmed the sustained PFS benefit of ibrutinib as first-line therapy for patients with CLL, including those with high-risk genomic features of unmutated IGHV (HR = 0.109) or del(11q) (HR = 0.033).[19]

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

Ibrutinib monotherapy was approved for first-line therapy for all patients based on the results of the RESONATE-2 study that established the efficacy of ibrutinib monotherapy as first-line therapy only in patients ≥65 years without del(17p).[19,115] The ECOG-ACRIN cancer research group [E1912) study and the FLAIR study [median age: 62 years; patients >75 years and >20% del(17p) cells were excluded] showed that ibrutinib + rituximab was more effective than FCR for patients ≤70 years without del(17p)/*TP53* mutation, especially for those with unmutated IGHV, indicating that ibrutinib may also be an appropriate option for younger patients with IGHV unmutated CLL.[22,24,116]

Ibrutinib is included with a category 1 recommendation for patients ≥65 years or younger patients with significant comorbidities as well as for patients <65 years without del(17p) or *TP53* mutation. The panel consensus to list ibrutinib under other recommended regimens is based on the toxicity profile. Randomized clinical trials demonstrated a more favorable toxicity profile for acalabrutinib and zanubrutinib (compared to ibrutinib).[114,117]

Ibrutinib + Obinutuzumab or Rituximab

Ibrutinib + obinutuzumab was approved by the FDA for first-line therapy based on the results of the iLLUMINATE study and there are no randomized clinical trials that compare ibrutinib versus ibrutinib + obinutuzumab.[74]

The E1912 and FLAIR studies showed that ibrutinib + rituximab was more effective than FCR for patients ≤70 years without del(17p)/*TP53* mutation, especially for those with unmutated IGHV, indicating that ibrutinib may also be an appropriate option for younger patients with IGHV unmutated CLL.[22,24] The results of two other randomized phase III trials confirmed that ibrutinib + rituximab is more effective than chemoimmunotherapy for previously untreated CLL without del(17p) or *TP53* mutation in patients ≥65 years or younger patients with comorbidities.[36,73,74,118] However, the addition of rituximab to ibrutinib did not result in improved clinical outcomes compared to ibrutinib monotherapy in these two randomized studies. In the Alliance North American Intergroup Study (A041202), the estimated 48-month PFS rates were 76% for both ibrutinib + rituximab and ibrutinib monotherapy.[36] In a single-center randomized study of 208 patients with high-risk CLL (27 patients with untreated CLL), at a median follow-up of 36 months, the estimated PFS rates were 86% and 87%, respectively, for ibrutinib and ibrutinib + rituximab.[118]

In all of the above mentioned randomized clinical trials that evaluated ibrutinib + rituximab or obinutuzumab, ibrutinib was given continuously until disease progression or intolerance and obinutuzumab or rituximab was added to the combination arm only for the first 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 + rituximab (for patients <65 years without significant comorbidities) and ibrutinib + obinutuzumab are included with a category 2B recommendation.

Ibrutinib + Venetoclax

The results of the CAPTIVATE study showed that fixed-duration treatment with ibrutinib + venetoclax results in improved PFS with high rates of durable response and uMRD4 across all patient subgroups.[78-80] In the fixed-duration cohort, with a median follow-up of 28 months, the estimated 24-month PFS rate was 95% for the overall study population [96% for patients without del(17p)/*TP53* mutation; 93% and 97%, respectively, for those with unmutated IGHV and mutated IGHV].[78] The estimated 24-month OS rates were 98% for the overall study population patients and also for patients without del(17p).

PFS was also significantly longer for ibrutinib + venetoclax compared to chlorambucil + obinutuzumab in the GLOW trial.[81,82] The 55-month follow-up data showed that ibrutinib + venetoclax was also associated with improved OS compared to chlorambucil + obinutuzumab.[83] The FLAIR study demonstrated that ibrutinib + venetoclax is also superior to FCR in terms of PFS in patients without del(17p)/*TP53* mutation.[85]

In the GLOW trial, ibrutinib + venetoclax was associated with significant toxicity (grade ≥3 adverse events occurred in 76% of patients and atrial fibrillation [any grade) was reported in 14% of patients) and treatment-related deaths were reported in 7% of patients.[81] Cardiac or sudden deaths during treatment occurred in patients with a CIRS score of ≥10 or an Eastern Cooperative Oncology Group performance-status score (ECOG PS) of 2 and with a history of hypertension, cardiovascular disease, and/or diabetes. This increase in toxicity may be related to the advanced age of patients enrolled in the study.

The combination of ibrutinib + venetoclax is not FDA approved for the treatment of CLL/SLL in the US. Based on the safety profile and the absence of data from randomized studies comparing this combination with other approved targeted therapies, the panel consensus was to include

ibrutinib + venetoclax as a category 2B recommendation under other recommended regimens.

Useful in Certain Circumstances

Chemoimmunotherapy

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

Fludarabine, Cyclophosphamide, and Rituximab

The FCR regimen results in high response rates and improved PFS and OS in specific subgroups of fit patients with previously untreated CLL, especially in those with mutated IGHV.[11,13,22,119]

FCR could be considered as a first-line therapy option for IGHV-mutated CLL in patients <65 years without significant comorbidities since the FCR regimen results in high response rates and improved PFS and OS in this specific subgroup of patients with previously untreated CLL, with a plateau on the PFS curve beyond 10 years.[11,13,119]

Bendamustine + Anti-CD20 Monoclonal Antibody

In the CLL10 study, although the PFS benefit of FCR was significant in physically fit patients <65 years, there was no significant difference in PFS between BR and FCR as first-line therapy for CLL without del(17p) in patients >65 years.[119] The incidence of severe neutropenia and infections was significantly more frequent in the FCR arm, especially among patients >65 years, and the incidences of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) were also significantly higher in the FCR arm.[119]

Bendamustine + anti-CD20 mAb (rituximab or obinutuzumab) may be a reasonable alternative for patients ≥65 years or younger patients with significant comorbidities.[119-121]

Obinutuzumab ± Chlorambucil

Given the favorable tolerability profile, obinutuzumab monotherapy or in combination with chlorambucil might be an acceptable treatment option for a small fraction of patients for whom more intensive regimens are not appropriate.[122-124]

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

High-dose methylprednisolone (HDMP) + Rituximab or Obinutuzumab

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).[125,126]

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

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

There are limited data from prospective clinical studies on the efficacy of covalent BTKis or BCL2 inhibitors as first-line therapy for patients with del(17p)/*TP53* mutated CLL. Patients with del(17p) CLL were not eligible for enrollment in the RESONATE-2 study, the E1912 study, the GLOW study, the FLAIR study, and the GAIA–CLL13 study.[19,22,24,27,81] Chemoimmunotherapy is contraindicated for del(17p)/*TP53* mutated CLL due to low response rates. Enrollment in an appropriate clinical trial is recommended for patients with untreated del(17p) CLL/SLL.

In the RESONATE-2 study, the OS benefit with ibrutinib was observed in patients with *TP53* mutation, del(11q), and/or unmutated IGHV and the estimated 5-year PFS rate was 56% for the group of 12 patients with *TP53* mutation.[19] However, comparison between ibrutinib and chlorambucil could not be made since only three patients in the chlorambucil group had *TP53* mutation.

In a phase II trial that included 34 treatment-naïve patients with *TP53* aberrations [32 patients with del(17p); 2 patients with *TP53* mutation without del(17p); median age 62 years], ibrutinib resulted in an ORR of 97% (30% CR; 64% PR; 3% PR-L) and the estimated 6-year PFS and OS were 61% and 79%, respectively.[127]

Results from the pooled analysis of clinical trials (PCYC-1122e, E1912, RESONATE-2, and iLLUMINATE) also confirmed the long-term safety and efficacy of ibrutinib as first-line therapy in patients with *TP53* aberrations.[128] With a median follow-up of 50 months, the estimated 4-year PFS and OS rates were 79% and 88%, respectively. The ORR was 93% (CR in 39% of patients). As mentioned above, the RESONATE-2 study, and the E1912 study excluded patients with del(17p) CLL and *TP53* mutation was identified retrospectively. Additionally, there are also data suggesting that *TP53* mutation in the absence of del(17p) also confers increased risk. However, it may not be as notable as that associated with the concurrent presence of *TP53* mutation and del(17p).[34]

In the CAPTIVATE study (n =159; 27 patients had del (17p) and/or TP53 mutation), the estimated 24-month PFS and OS rates for ibrutinib + venetoclax were 84% and 96%, respectively, for those with del(17p)/*TP53* mutation.[78]

In the ELEVATE-TN study, the PFS benefit for acalabrutinib ± obinutuzumab was seen across all patient subgroups including those with del(17p) or *TP53* mutation but only 14% of patients had del(17p) CLL.[20] In patients with del(17p) and/or *TP53* mutation, the estimated 72-month PFS rate was 56% for both acalabrutinib + obinutuzumab and acalabrutinib monotherapy, indicating no benefit with the addition of obinutuzumab to acalabrutinib. The estimated 72-month OS rates were 68%, 72%, and 53% for acalabrutinib, acalabrutinib + obinutuzumab, and chemoimmunotherapy, respectively.[113]

In the phase III SEQUOIA study, patients with del(17p) were not part of the randomized cohort but were enrolled only to single-agent zanubrutinib or, subsequently, to the combination of zanubrutinib and venetoclax.[21] In the prospectively enrolled non-randomized cohort [111 patients with del(17p)/*TP53* mutated CLL], single-agent zanubrutinib resulted in a higher ORR and statistically significant improvement in PFS compared to BR. The best ORR and 18-month PFS rates were 98% and 89%, respectively, for patients with high del(17p) (≥20%), and 92% and 88%, respectively, for patients with low del(17p) (>7% to <20%).[129]

In the CLL14 study, the PFS benefit for VenO was also seen across all patient subgroups including those with del(17p) or *TP53* mutation [del(17p) or mutated *TP53* were seen in only 8% and 12% of patients, respectively].[110]

Preferred Regimens

Given currently available data (as discussed above), acalabrutinib ± obinutuzumab, zanubrutinib, and venetoclax + obinutuzumab are included as preferred treatment options for first-line therapy with a category 2A recommendation.[20,21,110]

Other Recommended Regimens

Ibrutinib (category 1) and ibrutinib + venetoclax (category 2B) are included as options under other recommended regimens. The panel consensus to list ibrutinib under other recommended regimens is based on the toxicity profile.

Useful in Certain Circumstances

The panel emphasizes that the efficacy of BTKi-based regimens in del(17p) CLL exceeds that of the other regimens and BTKi-based regimens should be considered as the best choice in the absence of a contraindication to covalent BTKi.

HDMP + rituximab or obinutuzumab[125,126] or obinutuzumab[122] can be considered in selected circumstances when rapid disease debulking is needed or in a small fraction of patients in whom covalent BTKi and venetoclax-based regimens are contraindicated.

Second-Line and Subsequent Therapy

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

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

The efficacy data from randomized clinical trials that evaluated small-molecule inhibitors for relapsed/refractory CLL/SLL are discussed below and are summarized in Table 3.

BTK Inhibitors

Covalent BTK Inhibitors

Acalabrutinib, ibrutinib, and zanubrutinib are also approved for treatment of relapsed/refractory CLL/SLL based on the results of phase III randomized studies (ASCEND, ELEVATE-RR, RESONATE, and ALPINE trials).[114,117,130,131] The PFS benefit compared to chemoimmunotherapy was seen across all patient subgroups including those with del(17p) or *TP53* mutation.

In the ASCEND study, at a median follow-up of 47 months, the median PFS was 46 months and the 42-month PFS rate was 62% for patients with del(17p)/*TP53* mutation assigned to acalabrutinib.[130] The phase III ELEVATE-RR trial demonstrated that acalabrutinib is non-inferior to ibrutinib in terms of PFS and was also associated with a more favorable safety profile in patients with relapsed/refractory del(17p) or del(11q) CLL.[114]

The final analysis of the RESONATE study showed that the presence of del(17p)/*TP53* mutation or CK was not associated with inferior PFS outcomes to ibrutinib.[131] In an exploratory analysis that combined data from patients with del(17p) and *TP53* mutation, the median PFS was 41 months for patients with del(17p) and/or *TP53* mutation versus 57 months for those without del(17p) or *TP53* mutation. Similarly, the median PFS was 41 months for patients with CK compared to 45 months for those without CK. The phase II RESONATE-17 study established the efficacy and safety of ibrutinib in patients with relapsed or refractory del(17p) CLL

(n = 145), demonstrating an ORR of 83% (as assessed by the independent review committee).[132]

The randomized phase III study (ALPINE) showed that zanubrutinib resulted in a significantly higher ORR and significantly longer PFS in patients with relapsed/refractory CLL/SLL.[117] Zanubrutinib also resulted in a higher ORR and longer PFS across the major subgroups of patients, including those with a del(17p) and/or *TP53* mutation. Among patients with del(17p) and/or *TP53* mutation, the 36-month PFS rate was 60% for zanubrutinib and 44% for ibrutinib. The 3-year follow-up data also confirmed the superior efficacy and tolerability of zanubrutinib over ibrutinib.[133]

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

Non-Covalent BTK Inhibitor

Pirtobrutinib was approved for the treatment of patients with relapsed/refractory CLL/SLL who received at least two prior lines of therapy, including a BTKi and BCL-2 inhibitor, based on the results from the BRUIN study.[134,135]

In this phase I–II study, among the patients previously treated with a BTKi (n = 247), pirtobrutinib resulted in an ORR of 73% (82% including PR-L) and the median PFS was 20 months.[134] At a median follow-up of 23 months, the estimated 18-month OS rate was 81% for patients previously treated with a BTKi. In the subgroup of patients previously treated with the BTKi and venetoclax-based regimen (n = 100), the ORR was 70% (79% including PR-L) and the median PFS was 17 months.[134] The estimated median PFS was 17 months and 19 months, respectively, for patients with del(17p) or *TP53* mutation and those with unmutated IGHV.

The ORR (including PR-L) was higher irrespective of the status of prior therapy with BCL-2 inhibitors (83% for BCL-2 inhibitor naïve and 80% for BCL-2 inhibitor exposed); however, PFS was longer in the BCL-2 inhibitor-naïve group than in the BCL-2 inhibitor-exposed group (23 months and 16 months, respectively).[135] The 24-month OS rates were 83% and 61%, respectively.

Pirtobrutinib is included as an option (useful in certain circumstances; irrespective of del(17p)/*TP53* mutation) for patients with intolerance to prior covalent BTKi therapy or for those with disease that is resistant to covalent BTKi.[134,135] It is also an option (if not previously used; irrespective of del(17p)/*TP53* mutation) for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens.

BCL-2 Inhibitor

VenR is approved for the treatment of relapsed/refractory CLL/SLL based on the results of the phase III randomized MURANO trial.[87,136] VenR was superior to BR with longer PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation [HR = 0.21 for del(17p); HR = 0.25 for *TP53* mutation], and uMRD at the EOT was also higher for VenR (62% vs. 13% for BR).[87]

Venetoclax monotherapy resulted in an ORR of 77% (63% in patients who received prior therapy with a BTKi (ibrutinib) or PI3Ki (idelalisib) in patients with relapsed or refractory del(17p) CLL.[137] The estimated 24-month PFS and OS rates were 54% and 73%, respectively, for the overall study population (50% and 55%, respectively, for patients who had received prior BTKi or PI3Ki).

Venetoclax is also effective for relapsed/refractory CLL after prior treatment with ibrutinib or idelalisib,[138-141] although the results of a pooled analysis from four clinical trials showed that CLL refractory of BTKi or PI3Ki was significantly associated with lower CR rate and shorter duration of response (DOR).[142] Results from other retrospective analyses suggest that the use of venetoclax is associated with higher ORR and improved PFS following disease progression on ibrutinib (compared to disease progression on idelalisib) and also in patients who had received only one BTKi or PI3Ki (compared to those who had received >1 BTKi or PI3Ki).[143,144]

An international retrospective study showed that retreatment with the venetoclax-based regimen (Ven2) is feasible and effective for patients with CLL previously treated with a venetoclax-based regimen (Ven1) in any line of therapy.[145] Among 46 patients with CLL retreated with the venetoclax-based regimen (response data were available for 39 patients; a median of 16 months between the completion of Ven1 and initiation of Ven2), Ven2 resulted in an ORR of 80% (33% CR). At a median follow-up of 10 months, the median PFS was 25 months.

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

Retreatment with venetoclax ± anti CD20 mAb (VenO is preferred) is an option for disease relapse after a period of remission (if previously used as first-line therapy), irrespective of del(17p)/*TP53* mutation.[146]

Ibrutinib + Venetoclax

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

The panel consensus was to include ibrutinib + venetoclax as an option (other recommended regimens; irrespective of del(17p)/*TP53* mutation) with a category 2B recommendation based on the results of the CLARITY study.[89] This combination is also an option (category 2B) for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens (if not previously used; irrespective of del(17p)/*TP53* mutation).

PI3K Inhibitors

Idelalisib ± rituximab (IdR) and duvelisib also demonstrated efficacy (in terms of median PFS) in randomized phase III studies for patients with relapsed/refractory CLL/SLL.[147-152]

In a phase III randomized trial (220 patients; CIRS >6, decreased renal function, or cumulative marrow toxicity from prior therapy; randomized to receive IdR or rituximab + placebo), IdR demonstrated efficacy in patients relapsed/refractory CLL/SLL with and without del(17p). IdR significantly prolonged survival in patients with del(17p) or *TP53* mutation compared with those treated with rituximab + placebo but there was no difference in survival benefit compared to those without del(17p).[148] The median OS was 29 months for patients treated with IdR compared to 15 months for those treated with rituximab + placebo. IdR is FDA approved for relapsed/refractory CLL based on the results of this study and is available for clinical use with a black box warning regarding the risks of fatal and serious toxicities including hepatotoxicity, diarrhea, colitis, pneumonitis, and intestinal perforation.

Idelalisib monotherapy also demonstrated activity in relapsed/refractory SLL.[149] The indication for idelalisib monotherapy in relapsed/refractory SLL was withdrawn by the manufacturer as they are unable to complete the required confirmatory studies following the FDA accelerated approval. While the panel acknowledged the change in the regulatory status of idelalisib, the panel consensus was to continue listing idelalisib monotherapy as an option for relapsed/refractory SLL, given demonstrated efficacy.[149]

Duvelisib also significantly extended median PFS (17 months vs. 9 months) compared to ofatumumab in the subgroup of patients with del(17p).[150] 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.[152]

Duvelisib and idelalisib ± rituximab are included as options for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens (irrespective of del(17p)/*TP53* mutation status).

Chimeric Antigen Receptor (CAR) T-cell Therapy

Lisocabtagene maraleucel was approved for relapsed or refractory CLL/SLL after at least two prior lines of therapy, including a BTKi and a BCL-2 inhibitor (venetoclax), based on the results of TRANSCEND CLL 004 study.[153,154]

This study evaluated the safety and efficacy of lisocabtagene maraleucel in patients with relapsed or refractory CLL/SLL after ≥2 prior lines of therapy (N = 137; 117 patients received infusion with lisocabtagene maraleucel and all had received prior BTKi therapy. A subset of 70 patients also had received venetoclax-based regimens after disease progression on BTKi therapy). The primary efficacy analysis (49 patients including those had received prior venetoclax-based regimens after disease progression on BTKi therapy), reported an ORR of 43% (18% CR) as assessed by in independent review committee.[153] Among the 30 patients with del(17p) and/or *TP53* mutation, the ORR was 47% (23% CR).

The DOR was longer in patients achieving a CR. At the median follow-up was 20 months, the DOR was 35 months for all patients with responding disease (not reached for patients achieving a CR and 24 months for patients achieving a PR).[153] The median PFS and OS were 12 months and 30 months respectively. The median PFS was not reached in patients achieving a CR compared to 26 months for those achieving a PR and 4 months for those with non-responding disease). The uMRD (10^{-4} by NGS) rate was 63% in blood and 59% in the bone marrow.[153,154] The median PFS was longer in patients who had uMRD (26 months vs. 3 months for those with detectable MRD).[153] The 24-month follow-up data confirmed the high uMRD rates (64% in blood and 60% in the bone marrow) and longer DOR among patients achieving CR.[154] The median DOR was 30 months for all patients with responding disease and it was not reached for patients in CR.

Lisocabtagene maraleucel is a one-time infusion that does not require continuous treatment. It is included as an option for relapsed or refractory disease after prior therapy with BTKi- and venetoclax-based regimens (irrespective of del(17p)/*TP53* mutation).

Other Systemic Therapy Regimens

Chemoimmunotherapy regimens including FCR and BR demonstrated activity in patients with relapsed/refractory disease.[155-157]

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.[158,159]

Lenalidomide ± rituximab also demonstrated activity in patients with relapsed/refractory disease.[160-162] However, the ORR was lower for lenalidomide + rituximab in the subgroup of patients with fludarabine-refractory CLL compared with those with fludarabine-sensitive CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment.

Alemtuzumab + rituximab results in a higher ORR than that observed with alemtuzumab monotherapy.[163,164] 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.[165] Obinutuzumab (as monotherapy) also demonstrated activity in patients with relapsed/refractory CLL/SLL.[123]

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

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

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

Alemtuzumab ± rituximab, HDMP + anti-CD20 mAb, and lenalidomide ± rituximab are included as options for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens. These recommendations are based on results from retrospective analyses or subgroup analyses from prospective clinical trials that had included patients with del(17p) or *TP53* mutation. However, it should be noted that these studies were not sufficiently powered to evaluate the efficacy and safety of regimens in patients with del(17p) or *TP53* mutation.

Special Considerations for the Use of Small-Molecule Inhibitors

Management of Resistance to Small-Molecule Inhibitors

Covalent BTK Inhibitors

Acquired resistance to covalent BTKis is predominantly mediated by *BTK* and *PLCG2* mutations.[48,166] *BTK* and/or *PLCG2* mutations were detected at an estimated median of 9 months before progression in patients treated with ibrutinib, and these mutations were also detected in patients with progressive CLL during ibrutinib therapy up to 15 months before the manifestation of clinical progression.[48,167] *BTK* C481 mutations were also detected in 69% patients with disease relapse at an estimated median of 12 months before progression in patients treated with acalabrutinib.[166] Long-term follow-up is needed to confirm if *BTK* C481 mutations will emerge in patients treated with zanubrutinib. Venetoclax is effective for the management of relapsed/refractory CLL after prior treatment with ibrutinib or idelalisib.[138-144]

Testing for *BTK* mutations may be helpful to confirm resistance to BTKis. The reported VAF are variable, with low VAF often associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance.[48,167] Testing for *BTK* or *BCL2* mutations as screening for resistance to BTKi or venetoclax is not currently recommended. Testing for *BTK* and *PLCG2* mutations may be useful in patients with disease progression or no response while on BTKi therapy, including if poor treatment adherence is considered as a possible cause. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment in absence of disease progression.

Alternative covalent BTKi (acalabrutinib or zanubrutinib) is not a reasonable treatment option for patients with a mutation in either *BTK* or *PLCG2*. Pirtobrutinib is an effective option for the management of resistance to covalent BTKi, including in patients with *BTK* C481 mutations.[134,135] In the BRUIN study, mutations in *BTK, TP53*, and *PLCG2* were detected at baseline in 53%, 48%, and 14% of patients, respectively. Among the patients with *BTK* C481 mutation, decrease in *BTK* C481 VAF or complete clearance of *BTK* C481 clone was observed in 86% and 55% of patients, respectively.[168]

BCL-2 Inhibitors

Acquisition of *BCL2* mutations (G101V and D103Y) were implicated in resistance to venetoclax.[169,170] *BCL2* G101V mutation (low VAF) was identified in patients with progressive CLL during venetoclax therapy up to 25 months before clinical progression.[169] *BCL2* mutations are uncommonly associated with clinical resistance to venetoclax; therefore, other resistance mechanisms must be important.

Limited available data suggest that subsequent BTKi therapy or retreatment with venetoclax-based regimens is effective in patients with relapsed CLL following treatment with venetoclax, whereas PI3Ki following fixed-duration treatment with venetoclax does not appear to result in durable remissions.[145,171-173]

Management of Adverse Events

BTK Inhibitors

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

AEs associated with BTKi are discussed below and are summarized in Table 4.

Acalabrutinib and zanubrutinib both have a more favorable toxicity profile than ibrutinib due to the more selective/specific inhibition of BTK. In the ELEVATE-RR head-to-head trial of acalabrutinib versus ibrutinib, treatment discontinuation due to AEs was lower with acalabrutinib (15% vs. 21% for ibrutinib).[114,174] The incidences of AEs of special interest were also lower with acalabrutinib compared to ibrutinib: atrial fibrillation (9% vs. 16%), hypertension (9% vs. 23%), and bleeding (38% vs. 51%).[114,174] Acalabrutinib was associated with a higher rate of headache (35% vs. 20% for ibrutinib), with only 2% of patients experiencing grade ≥3 headache.[114] Headache is commonly observed with acalabrutinib early in the treatment course and can generally be managed with analgesics (eg, acetaminophen) and caffeine supplements and typically subsides with time on treatment.

Zanubrutinib was also associated with a lower rate of atrial fibrillation (grade ≥3; 2% vs. 4%) compared to ibrutinib in the ALPINE trial.[117] In contrast, neutropenia of any grade was more frequent with zanubrutinib (29% vs. 24% for ibrutinib); however, this did not translate into a higher rate of infection (71% with zanubrutinib vs. 73% for ibrutinib). The incidences of grade ≥3 infections were 27% and 28%, respectively.

Pirtobrutinib has a favorable toxicity profile (low incidences of atrial fibrillation, major hemorrhage, and hypertension) due to more selective inhibition of BTK and the relative absence of off-target inhibition.[134,135] Longer-term follow-up data are needed to assess the incidence of these AEs.

The benefit and risk of BTKis should be evaluated in patients requiring anti-platelet or anticoagulant therapies. Patients requiring the use of anticoagulants including warfarin were excluded from clinical trials evaluating acalabrutinib and ibrutinib while the use of anticoagulants including warfarin was not restricted in clinical trials evaluating zanubrutinib (except in the ALPINE trial). Zanubrutinib can be

coadministered with anticoagulants including warfarin. Concomitant administration of ibrutinib or acalabrutinib with warfarin should be avoided.

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

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

Switching to alternate covalent BTKi therapy can be considered in the setting of non-adherence or intolerance to therapy in the absence of disease progression, especially in patients with atrial fibrillation or hypertension that is not medically controllable. Acalabrutinib and zanubrutinib were shown to be effective for the management of disease in patients with ibrutinib intolerance.[117,175,176] Pirtobrutinib is also an acceptable option for the management of intolerance to covalent BTKi.[134,135] Limited data from real-world studies suggest that dose modification of ibrutinib may resolve intolerance without compromising efficacy.[177-180] In patients with no intolerance, ibrutinib can be continued until disease progression while following recommended dose modification guidance as needed. However, the efficacy of dose modification of ibrutinib was not confirmed in prospective studies.

BCL2 Inhibitor

TLS was an important side effect of venetoclax in early clinical trials. Initiation at lower dose (20 mg for one week) and gradual step-wise ramp-up over 5 weeks to target dose (400 mg daily) along with TLS prophylaxis is recommended to mitigate the risk and frequency of TLS.[181] Initiation and accelerated dose escalation (20–400 mg over 3 weeks) with close inpatient monitoring for TLS can be done in patients with high tumor burden and concern for rapid disease progression on or following BTKi therapy.[138,182,183] Recommendations for TLS prophylaxis based on tumor burden are outlined in the algorithm on CSLL-F.

Other AEs associated with venetoclax ± mAb are summarized in Table 5. Growth factor support should be considered for patients with neutropenia. Dose reduction may be necessary for patients with persistent neutropenia and limited bone marrow involvement.

PI3K Inhibitors

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

Hepatotoxicity is a major concern in younger patients treated with idelalisib as first-line therapy.[184] Close monitoring of transaminase levels is essential and concurrent administration of idelalisib or duvelisib with other hepatotoxic drugs should be avoided.

The addition of anti-CD20 mAb or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia.[185] Anti-infective prophylaxis for herpes simplex virus (HSV) and Pneumocystis jirovecii pneumonia (PJP), and monitoring for cytomegalovirus (CMV) reactivation are recommended for patients receiving idelalisib or duvelisib.

CAR T-cell Therapy

In the primary safety analysis of the TRANSCEND CLL 004 study, cytokine release syndrome (CRS) and neurologic events were the adverse events of special interest (AESI) reported in 85% (grade 3, 9%) and 45% (grade 3, 18%) of patients, respectively.[153] Headache (29%), confusional state (26%), and dizziness (25%) were the most common neurologic

events. Tocilizumab and/or corticosteroids were used in 67% and 33% of patients respectively, for the management of CRS and neurologic events. Neutropenia (60%), anemia (52%), thrombocytopenia (41%) and infections (17%), were the other most common grade ≥3 AEs. Second primary malignancies were reported in 9% of patients, but none were related to treatment with lisocabtagene maraleucel. The safety results after 24-month follow-up were similar to those reported in the primary safety analysis.[154]

CRS and neurologic toxicity should be managed based on the toxicity grade as outlined in the *Management of CAR T-Cell–Related Toxicities* section of the NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.

Allogeneic Hematopoietic Cell Transplant

Long-term results from several prospective studies showed that allogeneic hematopoietic cell transplant (HCT) can provide long-term disease control and also overcome the poor prognosis associated with del(17p) and *TP53* mutations.[38,186-192] 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.[193,194] 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 covalent BTKi as first-line therapy and the availability of venetoclax as an effective treatment option for relapsed or refractory CLL, allogeneic HCT is not considered as a reasonable treatment option for relapsed/refractory CLL after initial purine analogue-based therapy.[195]

Allogeneic HCT can be considered for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens in patients without significant comorbidities. HCT-specific comorbidity index (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.[196,197]

Histologic Transformation

Histologic transformation (also known as Richter transformation) of chronic lymphocytic leukemia (CLL) 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.[198-202] Clinical outcomes in patients with Richter's transformation to DLBCL are exceedingly poor with a pattern of no response to minimal responses to chemoimmunotherapy 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; $P < .001$).[203-206] 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.

Richter transformation to DLBCL is characterized by immunoblastic morphology and non-germinal center B-cell immunophenotype; however, cell of origin does not seem to have prognostic implications.[207] CD19, CD20, CD22, PAX5, MUM1, and LEF1 are the most commonly expressed immunohistochemical markers whereas CD5 and CD23 are variable.[207,208] 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:[209-216]

- Unmutated *IGHV* status
- Stereotyped BCR subset 8 combined with VH4-39 usage

- Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) such as del(17p) and complex karyotype (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.[215] Richter's transformation has also been reported following treatment with ibrutinib and venetoclax.[217-220] Unlike progressive CLL, Richter's transformation developing after treatment with ibrutinib lacked resistance to *BTK* and *PLCG2* mutations.[218] Progression on treatment, elevated LDH and lymphadenopathy without lymphocytosis were independent prognostic variables for Richter's transformation at progression in patients who received treatment with ibrutinib for CLL.[220] 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.[219] Further studies are needed to determine the exact risk profile and mechanism of Richter's transformation.

Accelerated CLL or CLL with expanded proliferation centers 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 may occur when there are increased prolymphocytes in the blood (>15%). Neither of these findings is considered as Richter's transformation, but rather as progression of CLL, associated with a more aggressive disease course and poorer outcomes.[201,202,221,222] Optimal management for these cases has not been established.

Diagnosis and Workup

The diagnosis of Richter 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 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.[105,223-225] 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 transformation from CLL among patients mostly treated with chemoimmunotherapy or chemotherapy.[220,226] In the aforementioned retrospective analysis of patients who developed Richter transformation after ibrutinib therapy, the median SUVmax was 15 for patients who developed Richter transformation compared with an SUVmax of 8 for those who did not develop Richter transformation.[220] However, other studies have reported that SUVmax greater than or equal to 10 alone lacks both sensitivity and specificity to distinguish Richter transformation from CLL in patients who develop Richter transformation while on ibrutinib.[227,228] In both these studies, biopsy proven Richter transformation was diagnosed in patients who had an SUVmax between 5 and 10, suggesting that PET alone is insufficient and lymph node biopsy is required for the definitive diagnosis of Richter transformation. Lymph node biopsy should be considered to rule out Richter transformation in patients with disease progression on ibrutinib, an elevated lactate dehydrogenase (LDH), or disease progression with lymphadenopathy without lymphocytosis.[220]

Epstein-Barr virus (EBV) infection has been reported in 16% of patients with Richter transformation and is associated with a poor outcome.[229] 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 transformation. However, RS-like cells in a background of CLL may progress to classical HL in some patients.[230] Biopsy specimen should be evaluated for EBV infection using LMP1 staining or EBV-encoded RNA in situ hybridization (EBER-ISH).

DLBCL arising from CLL/SLL can either be clonally related to underlying CLL/SLL (78%) or clonally unrelated to underlying CLL/SLL (22%).[214,231] Richter 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).[214] The majority of patients with Richter transformation to clonally related DLBCL carry unmutated IGHV.[231] 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.[214,231]

Richter Transformation to DLBCL

Richter transformation to clonally unrelated DLBCL should be managed as *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 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.[203] Elevated platelet counts, higher hemoglobin levels, lower beta-2-microglobulin and LDH levels have been identified as independent predictors of higher response rates to chemoimmunotherapy.[203] However, the use of these prognostic variables for selection of optimal first-line therapy for Richter transformation has not yet been established.

The regimens listed below are used at the NCCN Member Institutions based on published data (mostly from single-arm phase I/II studies; Table 6).

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)[232]
- R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)[233]
- R-hyper-CVAD (rituximab, cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone alternating with methotrexate and cytarabine) [234,235]
- OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab) [236,237]
- Venetoclax + RCHOP (category 2B)[238]

Allogeneic HCT can be considered for patients with disease responding to initial chemoimmunotherapy.[203,239-243] 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 complete response (CR) or partial response (PR) to initial therapy compared with those with disease responding to initial therapy but did not undergo allogeneic HCT, or who underwent allogeneic HCT for relapsed or refractory Richter transformation (75% vs. 27% and 21%, respectively; $P = .019$).[203] Treatment-sensitive disease and ≤3 previous lines of therapy were associated with superior progression-free survival (PFS) and overall survival (OS) outcomes following allogeneic HCT with reduced-intensity conditioning.[242]

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.[239,241] In a retrospective analysis that evaluated the outcome after autologous or allogeneic HCT in 59 patients with Richter 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.[239] In a multivariate analysis, chemotherapy-sensitive disease and reduced-intensity conditioning were found to be associated with superior RFS after allogeneic HCT. In a Center for International Blood and Marrow Transplant Research registry study evaluating outcomes after HCT (autologous HCT, n = 53; allogeneic HCT, n = 118), the 3-year PFS and OS rates were 43% and 52%, respectively, for patients who underwent allogeneic HCT. The corresponding 3-year PFS and OS rates were 48% and 57%, respectively, for patients who underwent autologous HCT. Deeper remissions at the time of transplant was associated with better survival outcomes after allogeneic HCT.[241]

There are no effective treatment options for patients with Richter transformation refractory to chemoimmunotherapy. Clinical trial is the preferred treatment option if available. In the absence of a suitable clinical trial, treatment recommendations as outlined for relapsed/refractory DLBCL in the NCCN Guidelines for B-Cell Lymphomas is an acceptable option for this group of patients.

Preliminary data from ongoing clinical trials suggest that PD-1 inhibitors (nivolumab and pembrolizumab) have promising activity in patients with Richter transformation.[244-247] The combination of nivolumab + ibrutinib has resulted in an ORR of 42% to 65% and the median PFS was 4 to 13 months in patients with Richter transformation.[244,245] The use of pembrolizumab in patients with Richter transformation as a single agent resulted in an ORR of 44% and the median PFS and OS were 5 months and 11 months, respectively.[246]

BTK inhibitors (BTKi; acalabrutinib and pirtobrutinib) have also demonstrated efficacy in the treatment of patients with pretreated Richter transformation.[248,249] In a phase I/II trial of 25 patients with Richter transformation (treatment naïve or previously treated), acalabrutinib (covalent BTKi) resulted in an ORR of 40% and the median PFS was 3 months.[46] In the BRUIN phase I/II study that included 57 patients with heavily pretreated Richter transformation (including prior therapy with chemoimmunotherapy and covalent BTKi), pirtobrutinib (non-covalent BTKi) resulted in an ORR of 54%.[249] At a median follow-up of 10 months, the median OS was 13 months.

The panel acknowledged that there are limited published data supporting the use of PD-1 inhibitors and BTKi in patients with Richter transformation refractory to chemoimmunotherapy or in patients with a del(17p)/*TP53* mutation and that additional data will be forthcoming. Few panel members felt that monotherapy with PD-1 inhibitors (nivolumab or pembrolizumab) is not an effective treatment option (outside of a clinical trial) for patients with relapsed or refractory Richter transformation, citing a report in which the use of PD-1 inhibitors in a non-trial population (10 patients with biopsy-proven Richter transformation to DLBCL treated with prior BTKi) was associated with poor efficacy with a short time to disease progression.[250] However, some panel members felt that given the unmet clinical need and the lack of effective treatment options, inclusion of PD-1 inhibitors (nivolumab and pembrolizumab) and BTKi (acalabrutinib and pirtobrutinib) as treatment options is reasonable for Richter transformation refractory to chemoimmunotherapy (especially in patients who are unable to receive chemoimmunotherapy regimens), based on the data discussed above. 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 or for patients who are unfit to receive intensive chemotherapy regimens.

Pirtobrutinib is included as an option for patients with del(17p) or *TP53* mutation or those with chemoimmunotherapy-refractory disease unable to receive alternative chemoimmunotherapy. Acalabrutinib, nivolumab, and pembrolizumab ± ibrutinib are included as options with a category 2B recommendation for the same patient population.

Richter Transformation to Hodgkin Lymphoma

Richter transformation to HL is clinically less aggressive than Richter transformation to DLBCL but it is associated with a poorer prognosis than de novo HL.[199,200,251,252] 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 transformation to HL.[253-255]

Richter transformation to HL should be managed as outlined in the NCCN Guidelines for Hodgkin Lymphoma.

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.[256,257] Patients with heavily pretreated fludarabine-refractory CLL have high susceptibility to developing serious infections.[258]

IVIG is associated with a significant decrease in the occurrence of infections but with no improvement in OS outcome.[259-263] Monitoring IVIG levels and monthly administration of IVIG (0.3–0.5 g/kg to maintain nadir 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.

Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation was reported in patients treated with chemotherapy ± immunotherapy agents.[264,265] HBV carriers have a high risk of HBV reactivation. Fulminant hepatitis, hepatic failure, and death associated with HBV reactivation occurred in patients receiving anti-CD20 mAb-containing regimens. Patients receiving IVIG may be HBcAb positive as a consequence of IVIG therapy.[266]

Antiviral prophylaxis and monitoring are recommended for patients receiving anti-CD20 mAb, alemtuzumab, purine analogs and idelalisib. 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.[267,268] Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. 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.[269]

HBV reactivation and invasive fungal infections were rarely reported in patients treated with ibrutinib.[270,271] There currently are no sufficient data to recommended routine screening and prophylaxis.

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.[272] Current practices 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.[273,274] Consultation with an infectious disease expert may be necessary.

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.[275,276] 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, some 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.[277] 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.[277-280] Purine analog-based therapy was associated with AIHA. Higher incidence of AIHA were reported in patients treated with fludarabine or chlorambucil compared to those who received fludarabine-based combination regimens.[277,281] 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.[282] 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.[282]

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine,[283] and splenectomy should be used in steroid-refractory cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias.[284-288] Eltrombopag and romiplostim are FDA-approved for the treatment of thrombocytopenia in patients with ITP that is refractory to steroids, IVIG, and splenectomy and were also shown to be effective in the management of CLL-associated ITP that is refractory to standard therapies.[289-293]

PRCA is less common in patients with CLL. PRCA can be managed with corticosteroids, cyclophosphamide, cyclosporine, or anti-thymocyte globulin.[276] Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. In 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.[276]

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.[294] 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).[295] Initiation of lenalidomide at lower doses (5, 10, or 15 mg/day) with

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.[296]

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.

Venous Thromboembolism

Lenalidomide may also be associated with venous thromboembolism (VTE) in patients with CLL/SLL.[297,298] 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.

Obinutuzumab infusion-related reactions (initial reaction and reactions in patients with high ALC) can be severe and patients should be monitored closely. Premedication with corticosteroid, antihistamine, and acetaminophen should be considered. Monitoring and prophylaxis for TLS is recommended for patients with high ALC.

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 or obinutuzumab). 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.[299,300] However, it is unclear if such a substitution poses the same risk of recurrence.

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.[301] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for intravenous rituximab in patients who received at least one full dose of intravenous rituximab without experiencing severe adverse reactions.

Immunizations

All live vaccines including live attenuated influenza vaccine should be avoided. Protein and conjugate vaccines were shown to induce better responses than plain polysaccharide vaccines.[302,303] The mRNA-based vaccines showed safety and efficacy against the SARS-CoV-2 infection (COVID-19) among immunocompetent individuals.[304] Studies that evaluated the safety and efficacy of mRNA-based vaccines in patients with hematological malignancies reported lower seroconversion rates and decreased antibody responses in patients with CLL/SLL, regardless of their treatment status.[305-309] The correlation, if any, between antibody titers against spike protein and the protective immunity in this population was not established, and the duration of any protection is unknown. Therefore, no recommendations can be made regarding antibody testing or actions based on antibody test results. Furthermore, tests are not available to assess cellular immunity post-COVID-19 vaccination.

Annual influenza vaccine, pneumococcal vaccine and COVID-19 vaccine are recommended for all patients as recommended by the CDC Guidelines. Zoster vaccine recombinant, adjuvanted is recommended for all patients treated with BTKi. Respiratory syncytial virus (RSV) vaccine (single dose) is recommended for all patients, including patients age <60 years.

Patients with CLL tend to have poor response to influenza vaccine and should be counseled to exercise care during influenza season even with vaccination. In the absence of laboratory testing to confirm immune response to mRNA-based vaccines, patients with CLL/SLL who received COVID-19 vaccines should take precautions recommended for unvaccinated individuals, such as mask wearing, social distancing, and diligent hand hygiene, until additional data are available to further clarify their risk.

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. In addition, the type of prior first-line therapy, duration of remission, and acquired resistance to treatment are also important factors in the selection of treatment for relapsed/refractory CLL/SLL.

Acalabrutinib ± obinutuzumab, zanubrutinib and VenO are preferred first-line therapy options for all patients including those with high-risk CLL/SLL (del(17p)/*TP53* mutation and unmutated IGHV). Acalabrutinib, zanubrutinib, and venetoclax ± rituximab are preferred treatment options for second-line and subsequent therapy. Ibrutinib is included as an option for previously untreated and relapsed/refractory CLL/SLL under other recommended regimens due to its toxicity profile compared to acalabrutinib and zanubrutinib. Pirtobrutinib is an effective alternative for the management of intolerance or resistance to a covalent BTKi and it is also an option for relapsed/refractory CLL/SLL after prior treatment with BTKi and venetoclax-based regimens. Lisocabtagene maraleucel is also an option for relapsed/refractory CLL/SLL after prior treatment with BTKi and venetoclax based regimens.

Venetoclax-based regimens are fixed-duration treatment options whereas BTKi are given continuously until disease progression or intolerance. The benefit/risk of continuous versus fixed-duration treatment approach should also be carefully evaluated.

Chemoimmunotherapy can be considered in selected circumstances (e.g. fit patients with IGHV-mutated CLL, in circumstances when rapid disease debulking is needed or in a small fraction of patients in whom BTKi and venetoclax-based regimens are contraindicated).

Histologic transformation of CLL to DLBCL or HL is associated with a poor prognosis. Precise diagnosis and enrollment in clinical trials evaluating novel targeted agents will improve the clinical outcomes of patients with histologic transformation.

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

Table 1: Undetectable MRD Rates for Venetoclax-based combinations regimens

Disease Setting	Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	Undetectable MRD ($\leq 10^{-4}$, uMRD4)	Method used for MRD detection
Previously Untreated CLL/SLL	**CLL14[26] (Phase III)**	**Venetoclax + obinutuzumab (VenO)**	216	≥65 years; (CIRS >6; CrCl <70 mL/min)	65 months	EOT+2: 75% (blood)	ASO-PCR; MRD-Flow; NGS
		Chlorambucil + obinutuzumab	216			EOT+2: 33% (blood)	
	CAPTIVATE[78] (Phase II; Fixed-duration cohort)	**Ibrutinib + venetoclax**	159	≤70 years; ECOG PS 0–1	28 months	EOT+3: 77% (blood); 60% (BM)	MRD-flow (8-color flow cytometry)
	CAPTIVATE[79] (Phase II; MRD cohort)	**Ibrutinib + venetoclax** (3 cycles of lead-in ibrutinib followed by 12 cycles of ibrutinib + venetoclax)	164	≤70 years; ECOG PS 0–1 (Prerandomization)	31 months	75% (blood); 68% (BM)	
		Ibrutinib + venetoclax	32	≤70 years; ECOG PS 0–1 (Randomization: uMRD not confirmed)		69% (blood); 66% (BM)	
		Ibrutinib	31			45% (blood); 42% (BM)	
	GLOW[82] (Phase III)	**Ibrutinib + venetoclax**	106	≥65 years or <65 years who also had CIRS >6 or CrCl <70 mL/min	34 months	EOT+3: 55% (blood); 52% (BM)	NGS
		Chlorambucil + obinutuzumab	105			EOT+3: 39% (blood); 17% (BM)	
	GAIA-CLL13[26] (Phase III)	**Ibrutinib + venetoclax + obinutuzumab**	231	≤65 years or >65 years [without del(17p) or *TP53* mutation]	39 months	15 months: 92% (blood); 78% (BM)	MRD-flow (4-color flow cytometry)
		VenO	229			15 months: 87% (blood); 73% (BM)	
		Venetoclax + rituximab (VenR)	237			15 months: 57% (blood); 43% (BM)	
		Chemoimmunotherapy (FCR ≤65 years; BR >65 years)	229			15 months: 52% (blood); 37% (BM)	
Relapsed or Refractory CLL/SLL	**MURANO (Phase III)[86]**	**VenR**	194	≥18 years; ECOG PS 0–1; adequate bone marrow, liver, and kidney function	36 months	62% (blood)	ASO-PCR and/or MRD-flow (4-color flow cytometry)
		Bendamustine + rituximab	195			13% (blood)	
	CLARITY[89] (Phase II)	Ibrutinib + venetoclax	53	Median age: 64 years ECOG PS 0–2	21 months	53% (blood); 36% (BM)	MRD-flow

Table 2: Phase III Randomized Studies of Small-Molecule Inhibitor Therapy for Treatment-Naïve CLL/SLL

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
ELEVATE-TN[20,113]	**Acalabrutinib**	179 [del(17p) and/or mutated *TP53,* n = 23]	≥65 years or <65 years with comorbidities (CIRS >6; CrCl <70 mL/min); ECOG PS of ≤2 and adequate hematologic, hepatic, and renal function	75 months	90% (11% CR)	Median: Not reached (72-month: 62%)	Median: Not reached (72-month: 76%)
	Acalabrutinib + obinutuzumab	179 [del(17p) and/or mutated *TP53,* n = 25]			96% (31% CR)	Median: Not reached (72-month: 78%)	Median: Not reached (72-month: 84%)
	Chlorambucil + obinutuzumab	177 [del(17p) and/or mutated *TP53,* n = 25]			83% (13% CR)	Median: 28 months (72-month: 17%)	Median: Not reached (72-month: 75%)
RESONATE-2[19]	**Ibrutinib**	136	≥65 years [without del(17p)]	8 years	92% (34% CR)	Median: Not reached (7-year: 59%)	Median: Not reached (7-year: 78%)
	Chlorambucil	133			37%	Median: 15 months (7-year: 9%)	Not reported
Alliance North American Intergroup (A041202)[36]	**Ibrutinib**	182	≥65 years	55 months	93% (7% CR)	4-year: 76%	4-year: 85%
	Ibrutinib + rituximab	182			94% (12% CR)	4-year: 76%	4-year: 86%
	Bendamustine + rituximab	183			81% (26% CR)	4-year: 47%	4-year: 84%
E1912 study[22,116]	**Ibrutinib + rituximab**	354	≤70 years	70 months	96% (17% CR)	5-year: 78%	5-year: 95%
	FCR	175			81% (30% CR)	5-year: 51%	5-year: 89%
SEQUOIA [without del(17p)][21]	**Zanubrutinib**	241 (mutated *TP53,* n =15)	≥65 years of age OR unsuitable for treatment with FCR (CIRS >6; CrCl <70 mL/min or a history of severe/multiple infections within 2 years); median age 70 years	27 months	95% (7% CR)	Median: Not reached (24-month: 86%; *P* < .0001)	Median: Not reached (24-month: 94%)
	Bendamustine + rituximab	238 (mutated *TP53,* n =13)			85% (15% CR)	Median: Not reached (24-month: 70%)	Median: Not reached (24-month: 95%)
SEQUOIA [with del(17p)][21]	**Zanubrutinib** (Non-randomized cohort)	111		31 months	90% (3% CR)	Median: Not reached (24-month: 89%)	Median: Not reached (24-month: 94%)

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Table 2 (continued): Phase III Randomized Studies of Small-Molecule Inhibitor Therapy for Treatment-Naïve CLL/SLL

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
CLL14[26,109]	**VenO**	216 [del(17p), n = 17; deleted or mutated *TP53*, n = 25]	≥65 years with comorbidities (CIRS >6; CrCl <70 mL/min)	65 months	85% (50% CR)	5-year: 63% (*P* < .0001)	5-year: 82%
	Chlorambucil + obinutuzumab	216 [del(17p), n = 14; deleted or mutated *TP53*, n = 24]			71% (23% CR)	5-year: 27%	5-year: 77%
GLOW[81,83]	**Ibrutinib + venetoclax**	106 (mutated *TP53*, n = 7)	≥65 years or <65 years who also had CIRS >6 or CrCl <70 mL/min	55 months	87% (39% CR)	54-month: 66%	54-month: 85%
	Chlorambucil + obinutuzumab	105 (mutated *TP53*, n = 2)			85% (11% CR)	54-month: 19%	54-month: 63%
GAIA-CLL13 [27,28]	**Ibrutinib + venetoclax + obinutuzumab**	231	≤65 years or >65 years [without del(17p) or *TP53* mutation]	51 months	94% (62% CR)	4-year: 96%	4-year: 95%
	VenO	229			96% (57% CR)	4-year: 90%	4-year: 95%
	Venetoclax + rituximab	237			93% (49% CR)	4-year: 70%	4-year: 96%
	Chemoimmunotherapy (FCR ≤65 years; BR >65 years)	229			81% (31% CR)	4-year: 62%	4-year: 94%
FLAIR[85]	**Ibrutinib + venetoclax**	260	Median age 62 years (>65 years, 31%) [without del(17p)]	44 months	87%	3-year: 97% 4-year: 94%	3-year: 98% 4-year: 95%
	FCR	263			76%	3-year: 77% 4-year: 65%	3-year: 93% 4-year: 87%

Table 3. Phase III Randomized Studies of Small-Molecule Inhibitor Therapy for Relapsed/Refractory CLL/SLL

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
ASCEND[130]	**Acalabrutinib**	155 [del(17p), n = 28; mutated *TP53,* n = 39]	Median age 67–68 years with ECOG PS ≤2 and adequate hematologic, hepatic, and renal function	47 months	83%	Median: Not reached 42-month: 62% (HR = 0.28; *P* < .0001)	Median: Not reached 42-month: 78%
	Idelalisib + rituximab (IdR) or Bendamustine + rituximab (BR)	155 (IdR, n = 119; BR, n = 36); [del(17p), n = 21; mutated *TP53,* n = 34]			84%	Median: 17 months 42-month: 23%	Median: Not reached 42-month: 65%
ELEVATE-RR[114]	**Acalabrutinib**	268	≥18 years; ECOG PS ≤2 and the presence of del(17p) and/or del(11q)	41 months	81% (3% CR)	Median: 38 months (for both treatment arms)	Median: Not reached (in either arm)
	Ibrutinib	265			77% (4% CR)		
RESONATE[131]	**Ibrutinib**	195 [del(17p), n = 63; mutated *TP53,* n = 79]	Median age 67 years	74 months	91% (11% CR)	Median: 44 months 60-month: 40%	Median: 68 months
	Ofatumumab	196 [del(17p), n = 64; mutated *TP53,* n = 68]			–	Median: 8 months 60-month: 3%	Median: 65 months
ALPINE[117,133]	**Zanubrutinib**	327 [del(17p) and/or mutated *TP53,* n = 41]	Median age 67 years; ECOG PS ≥1; relapsed/refractory disease after ≥1 prior systemic therapy	36 months	85% (10% CR)	36-month: 66% (HR = 0.67; *P* = .002)	36-month: 83%
	Ibrutinib	325 [del(17p) and/or mutated *TP53,* n = 38]			75% (7% CR)	36-month: 54%	36-month: 80%
MURANO[86,87]	**Venetoclax + rituximab**	194 [del(17p), n = 46; mutated *TP53,* n = 48]	≥18 years; ECOG PS 0–1; relapsed/refractory disease requiring therapy and adequate bone marrow, liver, and kidney function	59 months	92% (8% CR)	Median: 54 months (HR = 0.19; *P* < .0001)	5-year: 82% (HR = 0.40; *P* < .0001)
	Bendamustine + rituximab	195 [del(17p), n = 46; mutated *TP53,* n = 51]			72% (4% CR)	Median: 17 months	5-year: 62%

Table 4. Adverse Events of BTKis

Adverse Events	Treatment-Naïve CLL			Relapsed/Refractory CLL				
	ELEVATE-TN[20]	RESONATE-2[19]	SEQUOIA[21]	ELEVATE-RR[114]		ALPINE[117,133]		BRUIN[134]
	Acalabrutinib	Ibrutinib	Zanubrutinib	Acalabrutinib	Ibrutinib	Zanubrutinib	Ibrutinib	Pirtobrutinib
Most common adverse events (all grades)								
Diarrhea	40%	50%	14%	35%	46%	18%*	26%*	27%
Headache	38%	–	11%	35%	20%	NR	NR	17%
Cough	22%	36%	11%	29%	21%	13%	6%	24%
Fatigue	22%	36%	11%	20%	17%	–	–	32%
Arthralgia	20%	26%	14%	16%	23%	9%	14%	–
Anemia	–	26%	4%	22%	19%	13%	15%	–
Neutropenia	12%	13% (Grade ≥3)	16%	21%	25%	17% (Grade ≥3)*	16% (Grade ≥3)*	33%
Adverse events of special interest (AESI)								
Atrial fibrillation/Flutter								
Any grade	6%	16%	3%	9%	16%	6%*	16%*	4%
Grade ≥3	1%	5%	<1%	5%	3%	1%	2%	<1%
Bleeding								
Any grade	42%	NR	45%	38%	51%	36%	36%	43%
Grade ≥3	3%	NR	4%	–	–	3%	3%	1%
Major bleeding								
Any grade	4%	11%	5%	–	–	3%	4%	21%
Grade ≥3	3%	7%	4%	–	–	3%	3%	1%
Hypertension								
Any grade	7%	23%	14%	9%	23%	17%	16%	14%
Grade ≥3	3%	8%	6%	4%	9%	15%*	12%*	<1%
Infections								
Any grade	74%	26%	62%	–	–	31%*	31%*	71%
Grade ≥3	16%	–	16%	–	–	13%	18%	4%

*Data from extended follow-up

Table 5. Adverse Events of BCL2 Inhibitor-based regimens

Adverse Events (All Grades)	Treatment-Naïve CLL		Relapsed/Refractory CLL	
	CLL14[109]	GAIA-CLL13[27]	MURANO[136]	M13-982[137]
	VenO	VenO	VenR	Venetoclax
Neutropenia	58%	49%	61%	42%
Thrombocytopenia	24%	18%	13%	20%
Anemia	17%	8%	16%	25%
Infusion-Related reaction	45%	51%	8%	NR
Diarrhea	28%	33%	40%	39%
Nausea	19%	NR	22%	37%
Constipation	13%	NR	14%	NR
Pyrexia	23%	24%	15%	4%
Fatigue	15%	NR	18%	23%
Cough	16%	NR	18%	NR
Headache	11%	NR	11%	NR

Table 6: Chemoimmunotherapy for Richter Transformation

Regimen	No. of Patients	Median Follow-up	ORR	Median PFS	OS
RCHOP[232]	15	69 months	67% (7% CR)	10 months	Median: 21 months
REPOCH[233]	46	39 months	39%	4 months	Median: 6 months
R-hyper-CVAD[235]	30	8 months	43% (27% CR)	—	1-year: 28%
OFAR[236]	20	9 months	50%	—	6-month: 53%
Modified OFAR[237]	35	26 months	39% (7% CR)	—	Median: 7 months 2-year: 20%
Venetoclax + RCHOP[238]	26	6 months	68% (48% CR)	7 months	Median: 20 months

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