National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Version 5.2018 — March 26, 2018

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NCCN Guidelines Version 5.2018
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

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

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

Seema Bhat, MD † ‡
Roswell Park Cancer Institute

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

Danielle Brander, MD ‡
Duke Cancer Institute

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

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

Steve E. Coutre, MD ‡
Stanford Cancer Institute

Randall S. Davis, MD ‡
University of Alabama at Birmingham
Comprehensive Cancer Center

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

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

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

Manali Kamdar, MD ‡
University of Colorado Cancer Center

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

Nadia Khan, MD †
Fox Chase Cancer Center

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

Jeffrey Lancet, MD † ‡
Moffitt Cancer Center

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

Sami Malek, MD ‡
University of Michigan
Comprehensive Cancer Center

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

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

Tanya Siddiqi, MD ‡
City of Hope Comprehensive Cancer Center

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

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

Andrew D. Zelenetz, MD, PhD † Þ
Memorial Sloan Kettering Cancer Center

NCCN
Mary Dwyer, MS
Hema Sundar, PhD

[NCCN Guidelines Panel Disclosures]

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† Medical oncology
‡ Hematology/Hematology oncology
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Þ Internal medicine
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¥ Patient advocacy
* Discussion Writing Committee Member

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference

Updates in Version 5.2018 of the NCCN Guidelines for CLL/SLL from Version 4.2018 include:

MS-1

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

Updates in Version 4.2018 of the NCCN Guidelines for CLL/SLL from Version 3.2018 include:

Special Considerations for the Use of Small-Molecule Inhibitors

CSLL-F 2 of 3

- Venetoclax
  - 2nd bullet was revised from, "A more rapid dose escalation can occur (over 1 wk) for seriously ill patients with hospitalization and close inpatient monitoring for TLS. (Jones J, Mato A, Wierda W, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol 2018;19:65-75.)" to "Initiation and accelerated escalation of venetoclax (20 mg to 400 mg over 3-weeks) with close inpatient TLS monitoring can be done in the subgroup of patients with high tumor burden and where there is concern for rapid disease progression on or following BTK-inhibitor therapy. For accelerated escalation, venetoclax is administered at 20 mg on Week (W)1/Day (D)1, 50 mg on W1/D2-3, 100 mg on W1/D4-7 (all inpatient), then outpatient unless concern for TLS, 200 mg on W2/D1-7, and 400 mg on W3/D1-continuous. Additionally, continued BTK-inhibition concurrent with initiation and escalation of venetoclax with discontinuation of BTK-inhibitor when up to the venetoclax 400 mg daily dose can be considered. These agents can be given together safely." Reference 2 was added.

Updates in Version 3.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2018 include:

CSLL-D 1 of 5

- CLL/SLL without del(17p)/TP53 mutation:
  - First-line therapy options have been alphabetized under each category of preference and by each category of evidence and consensus.

CSLL-D 2 of 5

- CLL/SLL without del(17p)/TP53 mutation:
  - Relapsed/refractory therapy options have been alphabetized under each category of preference and by each category of evidence and consensus.
  - Relapsed/refractory therapy,
    - ◊ Preferred regimens,
      - – "Venetoclax + rituximab" was changed from a category 2A to a category 1 recommendation.
    - ◊ Other recommended regimens
      - – "Venetoclax" was moved from preferred to other and remains a category 2A recommendation.
      - – "Acalabrutinib" was added as a category 2A recommendation.
    - ◊ Footnote l was added, "Acalabrutinib should not be used for ibrutinib refractory CLL with BTK C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib without recurrence of these symptoms." Also for CSLL-D 3 of 5.
    - ◊ Footnote was removed, "Particularly for patients deemed intolerant or refractory to ibrutinib or idelalisib."

CSLL-D 3 of 5

- CLL/SLL with del(17p)/TP53 mutation:
  - First-line therapy and relapsed/refractory therapy options have been alphabetized under each category of preference and by each category of evidence and consensus.
  - Relapsed/refractory therapy,
    - ◊ Preferred regimens,
      - – "ibrutinib" was changed from a category 2A to a category 1 recommendation.
      - – "ventoclax + rituximab" was changed from a category 2A to a category 1 recommendation.
      - – "venetoclax" remains a preferred regimen and as a category 2A recommendation.
    - ◊ Other recommended regimens
      - – "Acalabrutinib" was added as a category 2A recommendation.

Special Considerations for the Use of Small-Molecule Inhibitors

CSLL-F 1 of 3

- Information regarding acalabrutinib was added.

CSLL-F 2 of 3

- Additional information regarding venetoclax was added.

CSLL-F 2 of 3

- "Co-administration with CYP3A Inhibitors and Inducers" was updated and "Co-administration with Gastric Acid Reducing Agents" was added.

Continued

Updates in Version 2.2018 of the NCCN Guidelines for CLL/SLL from Version 1.2018 include:

CSLL-D

- The NCCN Categories of Preference has been applied to the suggested treatment regimens.
  - The regimens are listed under two groups, "preferred regimens" and "other recommended regimens".
  - "In order of preference" was removed from all suggested treatment pages.

Updates in Version 1.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

General

- References were updated throughout the guidelines.
- New algorithm for Histologic Transformation (Richter's) and Progression was added. See HT-1.

CSLL-1

- Diagnosis, Essential
  - 1st bullet, "Rebiopsy Bone marrow aspirate with biopsy if consult material is nondiagnostic" was moved to the 3rd bullet.
  - 2nd bullet, 3rd sub-bullet was revised by moving "LEF1 may be useful to distinguish from MCL" from flow cytometry to the bullet related to IHC.
- Diagnosis, Informative for prognostic and/or therapy determination
  - Bullet, "Determination of CD38 and ZAP-70 expression by flow cytometry, methylation, or immunohistochemistry" was moved to footnote e and revised, "If not available, determination of CD38, CD49d, and ZAP-70 expression by flow cytometry, methylation, or immunohistochemistry may be obtained as surrogate markers for IGHV-mutation status. Evaluation ~~of ZAP-70 expression~~ of these markers can be challenging and ~~ZAP-70~~ is not recommended outside the setting of a clinical trial. IGHV mutation status is preferred over flow cytometry. ~~Methylation status is not widely available outside of a clinical trial.~~ IGHV mutation status is preferred over flow cytometry."
- For MBL, the bullet for absolute monoclonal B lymphocyte count <5000/mm^3, the count was changed to <5 x 10^9/L.

CSLL-2

- Workup, Useful Under Certain Circumstances
  - The following bullets were moved from Essential:
    - ◊ Hepatitis B testing ~~if CD20 monoclonal antibody~~ treatment contemplated
    - ◊ MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated
    - ◊ Pregnancy testing in women of child-bearing age (if *systemic therapy* or RT planned)
  - 3rd bullet was revised, "Chest/abdominal/pelvic CT *with contrast of diagnostic quality, if clinically indicated* ~~should be done prior to initiation of therapy (particularly when peripheral adenopathy is present and symptoms suggest bulky lymph nodes).~~" Corresponding footnote f was added.
  - 7th bullet was revised, "Unilateral bone marrow *aspirate* + biopsy ~~(± aspirate)~~ at initiation of therapy"

CSLL-2

- Footnote f was added, "Outside clinical trials, CT scans are not necessary for diagnosis, surveillance, routine monitoring for treatment response, or progression. May be warranted for symptoms or to evaluate bulky disease."
- Footnote g was revised, "Hepatitis B testing is indicated because of the risk of reactivation ~~with~~ *during treatment* ~~immunotherapy + chemotherapy~~ *(eg, immunotherapy, chemoimmunotherapy, chemotherapy,* ~~*or*~~ *targeted therapy)*."

CSLL-3

- Histologic transformation to diffuse large B-cell/ Hodgkin lymphoma, the recommendations were removed and is directed to the new Histologic Transformation (Ritcher's) and Progression algorithm. Corresponding footnotes were removed, "In addition to the regimens listed in Diffuse Large B-Cell Lymphoma, R-HyperCVAD has also been used in this setting." and "~~In addition to the regimens listed in Diffuse Large B-Cell Lymphoma, R-HyperCVAD has also been used in this setting.~~"
- For patients with adequate functional status, the recommendation was revised by adding "TP53 mutation status."
- Footnote p was revised, "Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] *and TP53 mutation status* is necessary ~~to direct~~ prior to initiation of treatment."
- Footnote j was added, "The dose is delivered in 1.8–2.0 Gy/fraction. See NCCN Guidelines for B-Cell Lymphomas, Principles of Radiation Therapy for additional details."

Continued

Updates in Version 1.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

CSLL-4

- CLL/SLL without del(17p)/TP53 mutation
  - Information for evaluating relapsed/refractory disease was added for Frail patients with significant comorbidity.

CSLL-5

- CLL/SLL without del(17p)/TP53 mutation, Age ≥65 y and younger patients with significant comorbidities and Age <65 y without significant comorbidities
  - Relapsed/Refractory Therapy
    - ◊ TP53 mutation status was added to the Re-evaluate bullet.
    - ◊ Bullet for "If histologic transformation or histologic progression of CLL, see HT-1" was added.
  - After Relapsed/Refractory Therapy,
    - ◊ "Clinical trial" was added
    - ◊ For "Consider allogeneic *HCT* ~~stem cell transplant,~~ if without significant comorbidities" the following clarification was added, "in patients with CLL refractory to small-molecule inhibitor therapy."

CSLL-6

- CLL/SLL with del(17p)/TP53 mutation
  - Response to Therapy
    - ◊ After response, the two criteria "complex karyotype present" and "complex karyotype not present" were removed. For complex karyotype present, the treatment options, "Consider allogeneic stem cell transplant or Clinical trial or Observe" were removed and "Consider allogeneic stem cell transplant" was moved under Relapsed/Refractory Therapy as "Consider allogeneic HCT if without significant comorbidities in patients with CLL refractory to ibrutinib."
    - ◊ After response, the algorithm now goes to "continue treatment with small molecule inhibitor" and then "Progression"
  - Relapsed/Refractory Therapy
    - ◊ Bullet for "If histologic transformation or histologic progression of CLLL, see HT-1" was added.

CSLL-A

- Prognostic Information for CLL/SLL
  - Table, "Immunoglobulin Heavy-Chain Variable (IGHV) Region Gene Mutation and Surrogates by Flow Cytometry" was revised by adding outcome associations for TP53 and CD49a.
- Footnotes
  - Footnote a was revised by removing, "Alemtuzumab or high-dose steroids have response in del(17p) disease."
  - Footnote b was revised by adding, "TP53 mutation status also provides additional prognostic information to FISH."
  - Footnote c was added, "IGHV mutation status is preferred over flow cytometry. Flow cytometry markers may be surrogate markers for IGHV mutation status. If not available, determination of CD38, CD49d, and ZAP-70 expression by flow cytometry may be used as a surrogate for IGHV mutation status. Evaluation of these markers can be challenging and is not recommended outside the setting of a clinical trial."

CSLL-B 1 of 2

- Rai system,
  - The description for Stage 0 was revised, "Lymphocytosis, lymphocytes in blood ~~*>15,000/mcL*~~ ~~*>5000 mcL*~~ *>5 x 10^9/L clonal B-cells* and >40% lymphocytes in the bone marrow."

CSLL-B 2 of 2

- SLL staging system
  - Footnote h was added, "Immune-mediated cytopenias are not the basis for these stage definitions."

CSLL-C 1 of 4

- Anti-infective prophylaxis
  - 1st bullet was revised, "Recommended *during treatment and thereafter (if tolerated)* for patients receiving purine-analog *or bendamustine-based chemoimmunotherapy*..."
  - 2nd bullet was extensively revised, "Clinicians must be aware of the high risk of CMV reactivation in patients receiving fludarabine-based chemoimmunotherapy, idelalisib, or alemtuzumab. The current appropriate screening is controversial. CMV viremia should be measured by PCR quantitation at least every 2–3 weeks. Some clinicians use ganciclovir (oral or IV) prophylactically if viremia is present; others use ganciclovir only if viral load is rising. Consultation with an infectious disease expert may be necessary."
  - 3rd bullet was revised, "HBV prophylaxis and monitoring is recommended in high-risk patients ~~receiving~~. See Treatment and Viral Reactivation below ~~anti-CD20 monoclonal antibodies alemtuzumab, purine analogs, and idelalisib. See Monoclonal Antibody Therapy and Viral Reactivation below for details on the management of infections~~.
- The heading "Monoclonal Antibody Therapy and Viral Reactivation" was changed to "Treatment and Viral Reactivation."
- A bullet related to the JC virus was added, "Progressive multifocal leukoencephalopathy can be seen in patients receiving treatment."

Continued

Updates in Version 1.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

CSLL-C 2 of 4

- Tumor lysis syndrome,
  - 1st bullet was revised, "Consider ~~tumor~~ *TLS* prophylaxis for patients ~~with bulky disease~~ at high risk for TLS, i*ncluding those with bulky disease and those with progressive disease after small-molecule inhibitor therapy*."
  - 2nd bullet, Laboratory hallmarks of TLS, "high LDH" was added.
  - 4th bullet, High-risk features
    - ◊ "Progressive disease after small-molecule inhibitor therapy" and "bulky lymph nodes" were added.
    - ◊ " Patients receiving treatment with venetoclax (See CSLL-G), chemoimmunotherapy, lenalidomide, and obinutuzumab" was added.
    - ◊ "Histologies of Burkitt lymphoma and Lymphoblastic lymphoma; occasionally patients with DLBCL and CLL" was removed.
    - ◊ "Bone marrow involvement" was removed.
  - 5th bullet, Treatment of TLS
    - ◊ First-line and at retreatment for hyperuricemia, the first sub-bullet was revised, "Allopurinol *or febuxostat* beginning 2–3 days prior to chemotherapy and continued for 10–14 days."

CSLL-C 3 of 4

- New section was added for "Cancer Screening: Standard screening guidelines should be closely followed for breast, colon, and prostate cancers."
- Rare Complications of Monoclonal Antibody Therapy, the bullet was revised by adding, "Re-challenge with the same monoclonal antibody in such settings is not recommended. It is unclear that re-challenge with alternative CD20 antibodies poses the same risk of recurrence."

CSLL-C 4 of 4

- Vaccination, 2nd bullet, "(live attenuated influenza vaccine should be avoided)" was added.

CSLL-D 1 of 5

- CLL/SLL without del(17p)/TP53 mutation:
  - First-line therapy, Frail patient with significant comorbidity (not able to tolerate purine analogs)
    - ◊ High-dose methylprednisolone (HDMP) + rituximab was added as a category 2B recommendation.
  - First-line therapy, Age ≥65 y and younger patients with significant comorbidities
    - ◊ Bendamustine ± rituximab was changed to Bendamustine ± *CD20 monoclonal antibody*
    - ◊ HDMP + rituximab was added as a category 2B recommendation.
  - First-line therapy, Age <65 y without significant comorbidities
    - ◊ The order of preference was revised.
    - ◊ HDMP + rituximab was added as a category 2B recommendation.
    - ◊ PCR (pentostatin, cyclophosphamide, rituximab) was changed from a category 2A to a category 3 recommendation.
    - ◊ Bendamustine ± rituximab was changed to Bendamustine ± *CD20 monoclonal antibody*
  - Post First-line Maintenance Therapy
    - ◊ Bullet was revised, "Consider lenalidomide maintenance for high-risk patients (*blood* MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated IGHV) after first-line therapy."
- Footnotes
  - Footnote d was revised by adding, "CD20 monoclonal antibodies include: rituximab, ofatumumab, or obinutuzumab."
    - ◊ Footnote e was added, "Minimal residual disease (MRD) evaluation in blood with 10^{-4} sensitivity according to standardized ERIC method.") Also for CSLL-D 2 of 5 and 3 of 5)
    - ◊ Footnote h was added, "Rituximab and hyaluronidase human injection for subcutaneous use may be used for CLL in combination with fludarabine and cyclophosphamide (FC) regimen after patients have received at least one full dose of a rituximab product by intravenous route."
    - ◊ Footnote i was revised by adding, "Outcomes for CLL with del11q are better with chemoimmunotherapy containing an alkylating agent."

Continued

Updates in Version 1.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

CSLL-D 2 of 5

- CLL/SLL without del(17p)/TP53 mutation:
  - Relapsed/refractory therapy, Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities
    - ◊ The order of preference was revised.
    - ◊ Bendamustine ± rituximab was changed to bendamustine + rituximab and added to bullets for ibrutinib and idelalisib as follows along with the dosing for bendamustine
      - – Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated), rituximab ± ibrutinib (category 2B). This recommendation was changed from a category 3 to a category 2B recommendation.
      - – Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated), rituximab ± idelalisib (category 3)
  - Relapsed/refractory therapy, Age <65 y without significant comorbidities
    - ◊ The order of preference was revised.
    - ◊ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) was removed.
    - ◊ OFAR (oxaliplatin, fludarabine, cytarabine, rituximab) was removed.

CSLL-D 3 of 5

- CLL/SLL with del(17p)/TP53 mutation:
  - First-line therapy
    - ◊ Obinutuzumab + chlorambucil (category 3) was changed to obinutuzumab monotherapy with a category 2A recommendation.
  - Relapsed/refractory therapy
    - ◊ OFAR (oxaliplatin, fludarabine, cytarabine, rituximab) was removed.
  - Post First-line Maintenance Therapy
    - ◊ Bullet was revised, "Consider lenalidomide maintenance for high-risk patients (*blood* MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated IGHV or del(17p)/TP53 mutation) after first-line therapy and a corresponding foonote was added, "MRD evaluation with a sensitivity of 10^{-4} sensitivity according to the standardized ERIC method." This was changed from a category 2A to a category 3 recommendation.

Special Considerations for the Use of Small-Molecule Inhibitors

CSLL-F

- Ibrutinib,
  - 4th bullet, atrial fibrillation,
    - ◊ 3rd sub-bullet was revised, "*If uncontrolled,* consider switching to alternate therapy."
    - ◊ 4th sub-bullet was added, "If switching to venetoclax, assess risk for TLS."
    - ◊ Sub-bullet was removed, "Patients with recurrent atrial fibrillation that is not medically controllable should be changed to idelalisib."
  - Last bullet was revised, "Testing for *BTK* and *PLCG2* mutations may be useful ~~to identify patients receiving ibrutinib potentially at risk for clinical progression~~ *in patients receiving ibrutinib and suspected of having progression. BTK and PLCG2 mutation status alone is not an indication to change treatment."*
- Idelalisib,
  - 4th bullet was revised, "CMV *reactivation*: ~~Monitor per institutional guidelines or consult with Infectious Disease~~. *See CSLL-C.*"
  - 5th bullet was added, "PJP: ~~recommend bactrim or equivalent for PJP~~ prophylaxis with sulfamethoxazole/trimethoprim or equivalent."

- The following was added regarding venetoclax,
  - Dosage
    - ◊ The recommended dose of venetoclax is 400 mg PO daily until disease progression or unacceptable toxicity.
    - ◊ Initiate venetoclax at 20 mg for one week and gradually escalate to target dose of 400 mg PO daily over 5 weeks to reduce the risk of tumor lysis syndrome. See CSLL-G for recommended TLS prophylaxis and monitoring based on tumor burden.
    - ◊ Consider re-initiating at a lower dose then continue with dose escalation, in patients who have treatment interruption for >1 week during escalation.

CSLL-G

- A new bullet was added to the top of the page, "Patients with CrCl <80 mL/min and medium tumor burden, consider management as high risk for TLS."
- Bullet, "Initiate venetoclax at 20 mg dose for one week and gradual step wise ramp-up over 5 weeks to target dose of 400 mg daily," was moved to CSLL-F 2 of 2.
- In the table, for prophylaxis with high tumor burden, "febuxostat" was added as an option to the 2nd bullet with allopurinol.
- Footnote b was revised, "Lymph node size should be evaluated by *chest/abdominal/pelvic* CT scan *with contrast*."

DIAGNOSIS[a]

ESSENTIAL:

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

CLL/SLL → **See Workup for CLL/SLL (CSLL-2)**

Monoclonal B-cell lymphocytosis (MBL)
- **Absolute monoclonal B lymphocyte count <5 x 10^9/L**
- **All lymph nodes <1.5 cm**
- **No anemia**
- **No thrombocytopenia**

→ **Observe**

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:[d]

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

[a]CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-cell prolymphocytic leukemia (B-PLL) are excluded from this guideline.

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

[c]Absolute monoclonal B lymphocyte count <5000/mm^3 in the absence of adenopathy or other clinical features of lymphoproliferative disorder is MBL. Cells of same phenotype may be seen in reactive lymph nodes; therefore, diagnosis of SLL should only be made when effacement of lymph node architecture is seen.

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

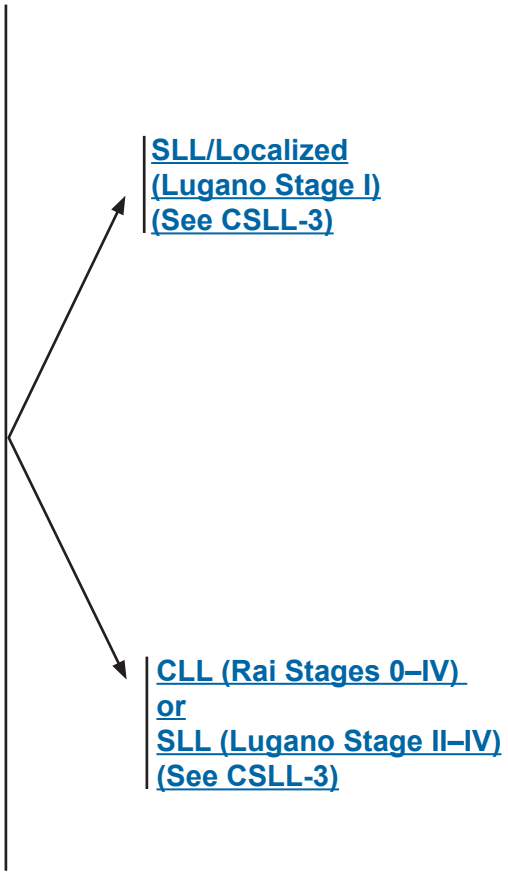
[e]If not available, determination of CD38, CD49d, and ZAP-70 expression by flow cytometry, methylation, or immunohistochemistry may be obtained as surrogate markers for IGHV-mutation status. Evaluation of these markers can be challenging and is not recommended outside the setting of a clinical trial.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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

WORKUP

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

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct Coombs' test
- Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated[f]
- Beta-2-microglobulin
- LDH
- Uric acid
- Unilateral bone marrow aspirate + biopsy at initiation of therapy
- Hepatitis B testing[g] if treatment contemplated
- MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age if systemic therapy or RT planned
- Discussion of fertility issues and sperm banking
- PET/CT scan to direct nodal biopsy, if histologic transformation is suspected. See HT-1.



[f]Outside clinical trials, CT scans are not necessary for diagnosis, surveillance, routine monitoring of treatment response, or progression. May be warranted for symptoms or to evaluate bulky disease.

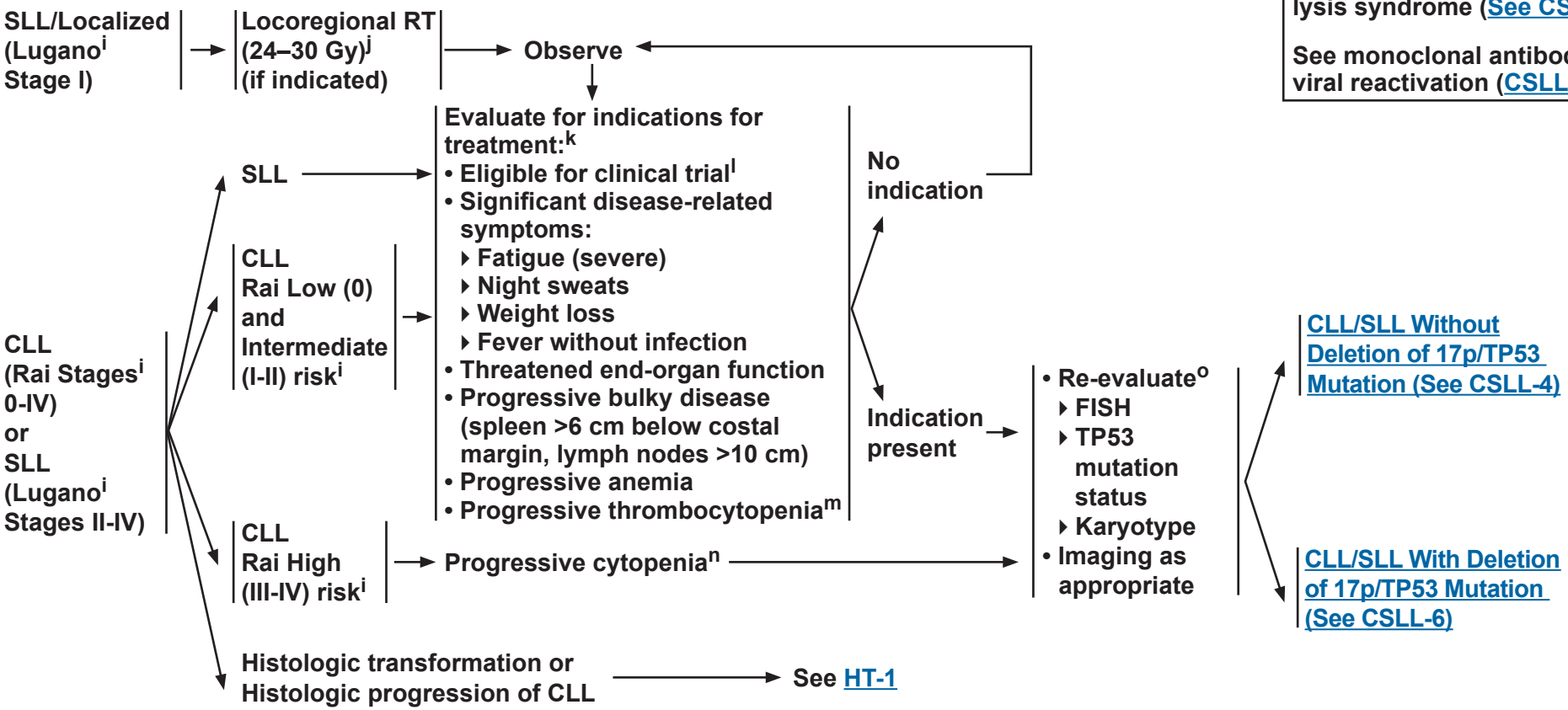
[g]Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRESENTATION[h]

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

See monoclonal antibody and viral reactivation (CSLL-C)



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

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

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

[k]Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.

[l]Given incurability with conventional therapy, consider including clinical trial as first-line therapy.

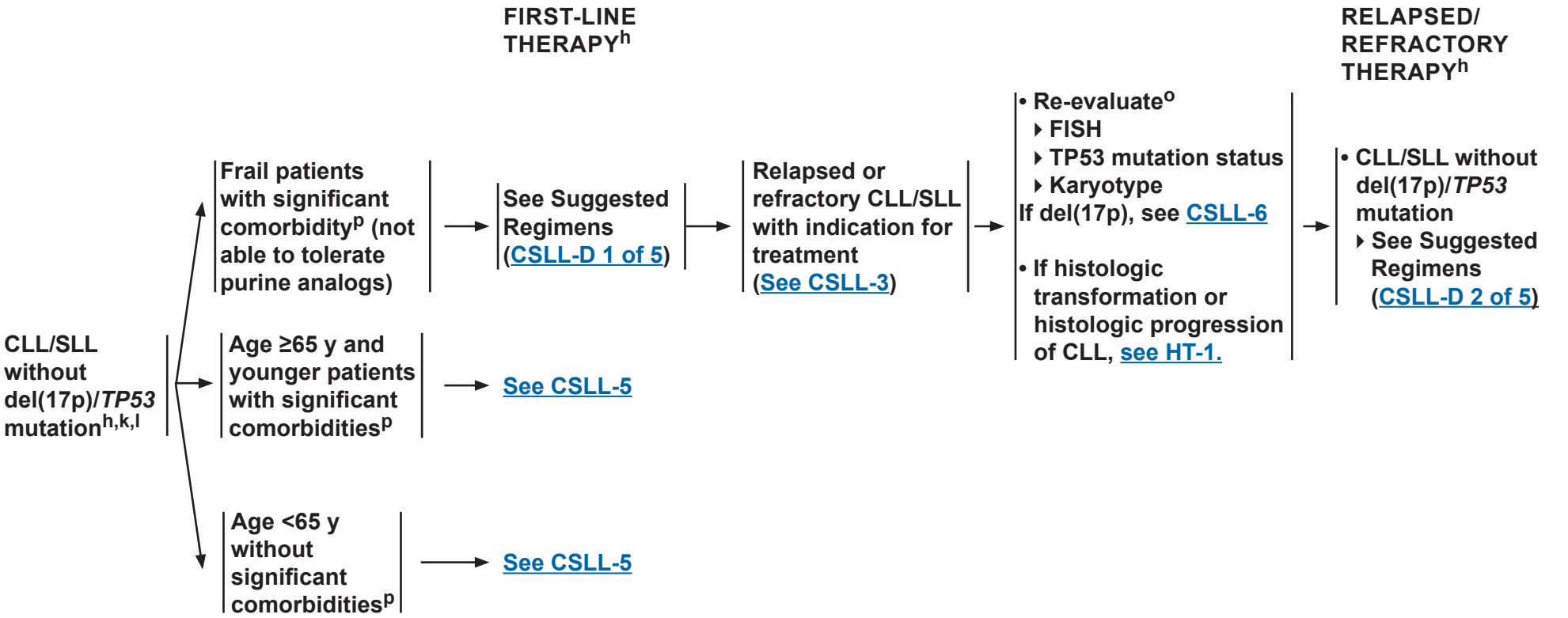
[m]Platelet counts >100,000 cells/mm^3 are typically not associated with clinical risk.

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

[o]Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] and TP53 mutation status is necessary prior to initiation of treatment.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CLL/SLL WITHOUT DELETION OF 17P/*TP53* MUTATION[h,k,l]



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

See monoclonal antibody and viral reactivation (CSLL-C)

[h] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[l] Given incurability with conventional therapy, consider including clinical trial as first-line therapy.
[o] Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] and TP53 mutation status is necessary prior to initiation of treatment.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

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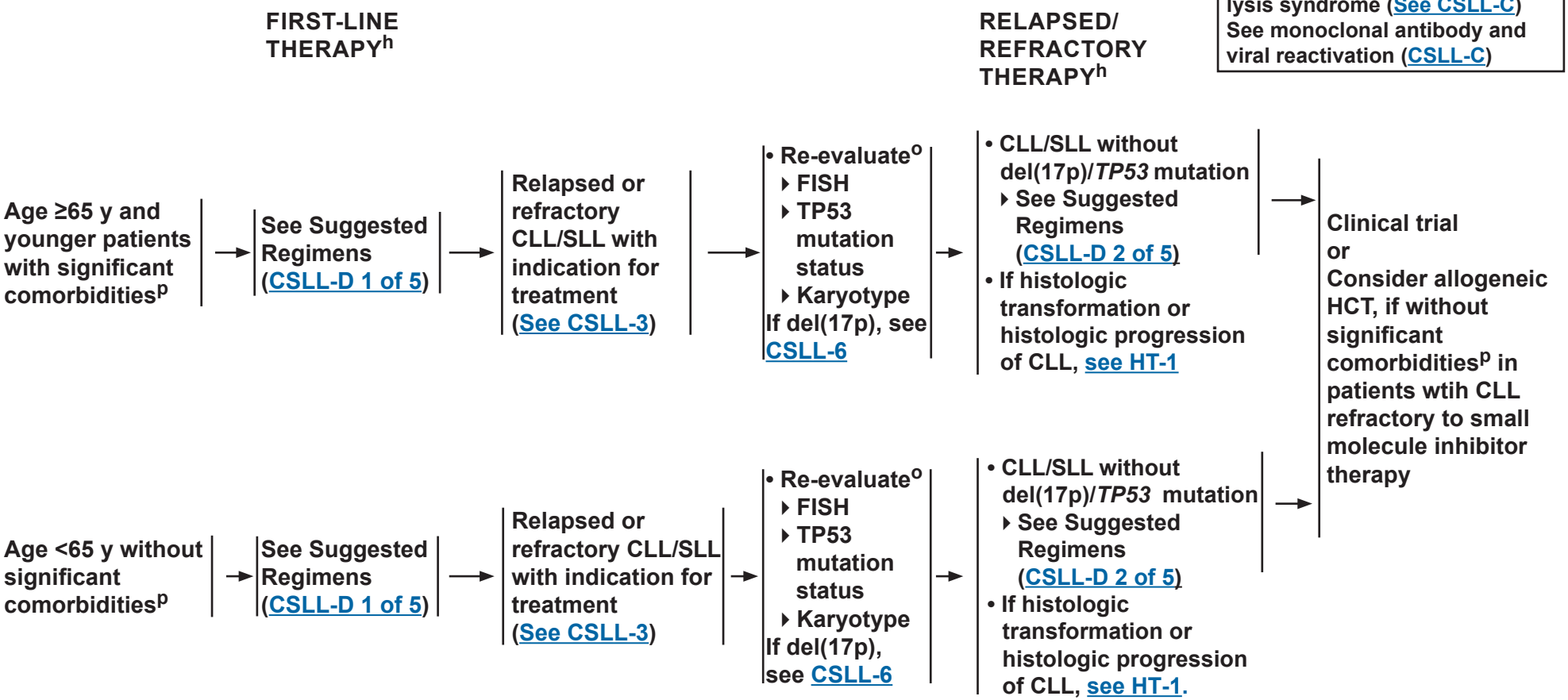
CLL/SLL WITHOUT DELETION OF 17P/*TP53* MUTATION[h,k,l]

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



[h] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[l] Given incurability with conventional therapy, consider including clinical trial as first-line therapy.
[o] Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] and TP53 mutation status is necessary prior to initiation of treatment.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

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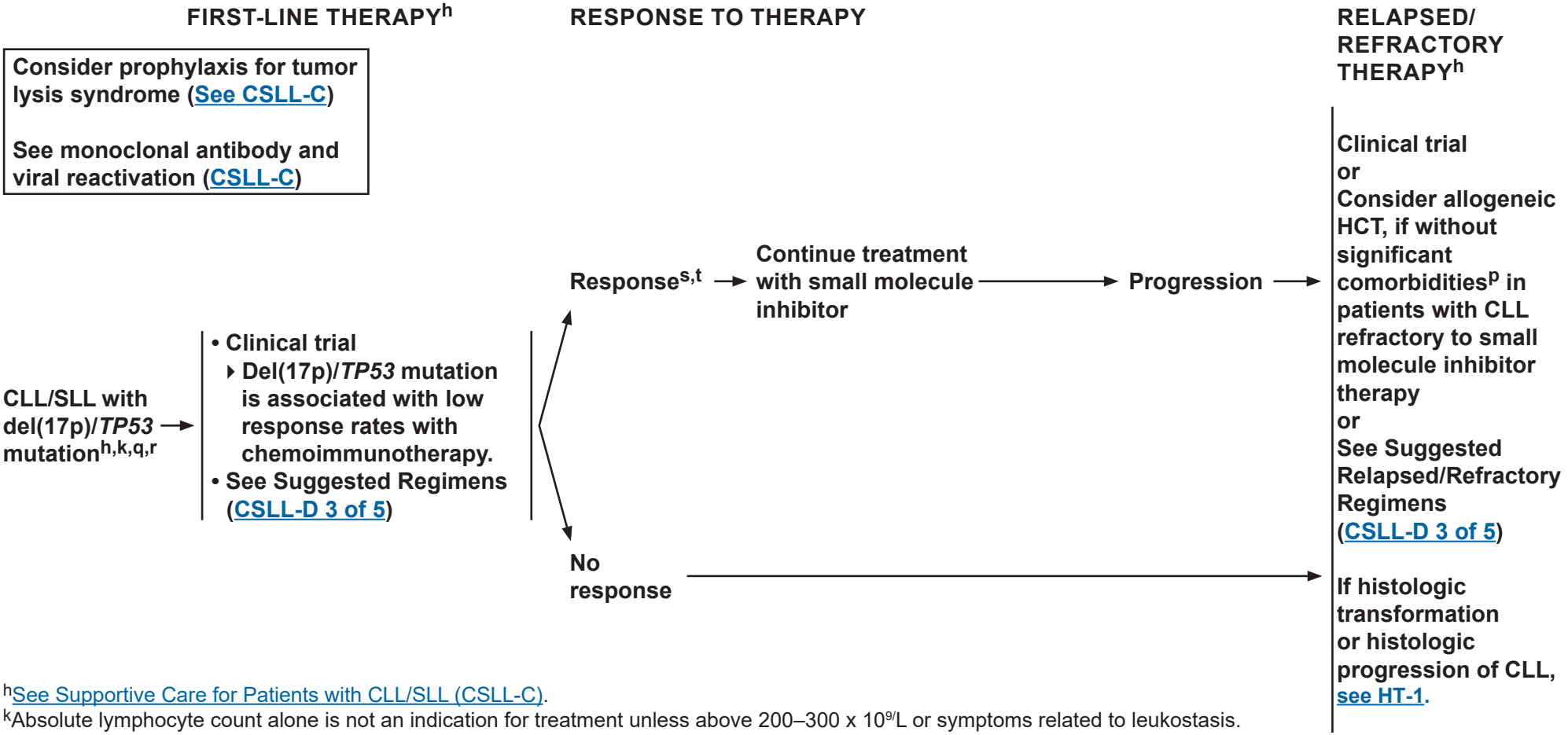
CLL/SLL WITH DELETION OF 17P/*TP53* MUTATION[h,k,q,r]



[h] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.
[q] CPG-stimulated karyotype is useful to identify high-risk patients, particularly for Bruton's tyrosine kinase (BTK) inhibitor therapy.
[r] Patients with low positivity should be retested due to chance of false-positive results.
[s] See Response Definition after Treatment for CLL/SLL (CSLL-E).
[t] For patients with complex karyotype (≥3 abnormalities) in achieving remission with or after BTK-inhibitor therapy, consider discussion of allogeneic HCT although data available do not support this as highly effective (Jaglowski et al. Br J Haematol 2012;159:82-87).

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PROGNOSTIC INFORMATION FOR CLL/SLL[a]

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

	Favorable	Unfavorable
DNA sequencing[b]		
TP53	**Wild-type**	**Mutated**
IGHV	**>2% mutation**	**≤2% mutation**
Flow Cytometry[c]		
CD38	**<30%**	**≥30%**
Zap 70	**<20%**	**≥20%**
CD49d	**<30%**	**≥30%**

Interphase Cytogenetics (FISH)[d]

Unfavorable	Neutral	Favorable
del(11q) **del(17p)**	**Normal** **+12**	**del(13q) (as a sole abnormality)**

Complex karyotype[e]

Unfavorable
≥3 unrelated chromosome abnormalities in more than one cell on karyotype

[a]This table provides useful prognostic information relative to the time to progression, where therapy is required, and survival. The presence of del(11q) and/or del(17p) are associated with short progression-free survival with chemotherapy and chemoimmunotherapy approaches.
[b]*IGHV* rearrangements involving VH3-21 carry a poor prognosis even if mutated. *TP53* mutation status also provides additional prognostic information to FISH.
[c]*IGHV* mutation status is preferred over flow cytometry. Flow cytometry markers may be surrogate markers for *IGHV* mutation status. If not available, determination of CD38, CD49d, and ZAP-70 expression by flow cytometry may be used as a surrogate for *IGHV* mutation status. Evaluation of these markers can be challenging and is not recommended outside the setting of a clinical trial.
[d]Formal studies identifying the percentage of abnormal cells identified by FISH are ongoing, although populations less than 10% appear to not have the clinical impact as noted in the table.
[e]Complex karyotype is based on results of conventional karyotyping of stimulated CLL cells.

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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 >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/mcL	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, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. (c) The American Society of Hematology.
[b]From: Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.
[c]Immune-mediated cytopenias are not the basis for these stage definitions.

Continued

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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[h]	**Nodes on both sides of the diaphragm**	**Not applicable**
	Nodes above the diaphragm with spleen involvement	
Stage IV[h]	**Additional non-contiguous extralymphatic involvement**	**Not applicable**

[d]Extent of disease is determined by PET/CT for avid lymphomas, and CT for non-avid histologies.
[e]Categorization of A versus B has been removed from the Lugano Modification of Ann Arbor Staging System.
[f]Whether II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.
[g]Note: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
[h]Immune-mediated cytopenias are not the basis for these stage definitions.

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Anti-infective Prophylaxis

- Recommended during treatment and thereafter (if tolerated) for patients receiving purine-analog or bendamustine-based chemoimmunotherapy, idelalisib, and/or alemtuzumab
  - Herpes virus prophylaxis with acyclovir or equivalent
  - PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent
- Clinicians must be aware of the high risk of CMV reactivation in patients receiving fludarabine-based chemoimmunotherapy, idelalisib, or alemtuzumab. The current recommendations for appropriate screening is controversial. CMV viremia should be measured by PCR quantitation at least every 2–3 weeks. Some clinicians use ganciclovir (oral or IV) prophylactically if viremia is present; others use ganciclovir only if viral load is rising. Consultation with an infectious disease expert may be necessary.
- HBV prophylaxis and monitoring is recommended for high-risk patients. See Treatment and Viral Reactivation below.

Treatment and Viral Reactivation

Hepatitis B virus (HBV):

- Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) testing for all patients receiving anti-CD20 antibody therapy
  - Quantitative hepatitis B viral load by PCR and surface antibody only if one of the screening tests is positive
- Note: Patients receiving IV immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy.

Treatment and Viral Reactivation *(continued)*

- Prophylactic antiviral therapy with entecavir is recommended for any patient who is HBsAg-positive and receiving treatment. If there is active disease (PCR+), it is considered treatment/management and not prophylactic therapy. In cases of HBcAb positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load.
  - Entecavir is preferred (Huang YH, et al. J Clin Oncol 2013;31:2765-2772; Huang H et al. JAMA 2014;312:2521-2530.)
  - Avoid lamivudine due to risks of resistance development.
  - Other antivirals including adefovir, telbivudine, and tenofovir are proven active treatments and are acceptable alternatives.
  - Monitor hepatitis B viral load with PCR monthly through treatment and every 3 months thereafter
    - ◊ If viral load is consistently undetectable, treatment is considered prophylactic
    - ◊ If viral load fails to drop or previously undetectable PCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy
  - Maintain prophylaxis up to 12 mo after oncologic treatment ends
    - ◊ Consult with hepatologist for duration of therapy in patient with active HBV

Hepatitis C virus (HCV):

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

JC virus

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

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Tumor Lysis Syndrome (TLS)

- Consider TLS prophylaxis for patients at high risk for TLS, including those with bulky disease and those with progressive disease after small-molecule inhibitor therapy.

- 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.

- High-risk features
  - Patients receiving treatment with venetoclax (See CSLL-G), chemoimmunotherapy, lenalidomide, and obinutuzumab
  - Progressive disease after small-molecule inhibitor therapy
  - Bulky lymph nodes
  - Spontaneous TLS
  - Elevated WBC
  - Pre-existing elevated uric acid
  - Ineffectiveness of allopurinol
  - 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 is essential
  - First-line and at retreatment for hyperuricemia
    - ◊ Allopurinol or febuxostat beginning 2–3 days prior to chemotherapy and continued for 10–14 days
      or
      Rasburicase is indicated for patients with any of the following risk factors:
      - presence of any high-risk feature
      - urgent need to initiate therapy in a high-bulk patient
      - situations where adequate hydration may be difficult or impossible
      - Acute renal failure
    - ◊ One dose of rasburicase is frequently adequate. Doses of 3–6 mg are usually effective.[a] Redosing should be individualized.
  - If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

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

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Continued

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Autoimmune Cytopenias

- Autoimmune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT
  - AIHA that develops in setting of treatment with fludarabine: stop, treat, and avoid subsequent fludarabine
- Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets
- Pure red cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation
- Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP)

Blood Product Support

- Transfuse according to institutional or published standards
- Irradiate all blood products to avoid transfusion-associated GVHD

Cancer Screening

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

Non-Melanomatous Skin Cancer

- Patients with CLL/SLL have a higher risk of developing non-melanomatous skin cancers
- Risk factors include caucasians and a history of intensive sun exposure at a young age
- For patients at-risk, annual dermatalogic skin screening is recommended

Rare Complications of Monoclonal Antibody Therapy

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

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,
  - adjust dose/interval to maintain nadir level of approximately 500 mg/dL

Rituximab Rapid Infusion

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

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Thromboprophylaxis

- Recommended for prevention of thromboembolic events in patients receiving lenalidomide:
  - Aspirin 81 mg 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 recommended for patients receiving lenalidomide
- Tumor flare reactions:
  - Painful lymph node enlargement or lymph node enlargement with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash
- Treatment:
  - Steroids (eg, prednisone 25–50 mg PO for 5–10 days)
  - Antihistamines for rash and pruritus (cetirizine 10 mg PO once daily or loratadine 10 mg PO daily)
- Prophylaxis:
  - Consider in patients with bulky lymph nodes (>5 cm)
  - Steroids (eg, prednisone 20 mg PO for 5–7 days followed by rapid taper over 5–7 days)

Use of Small-Molecule Inhibitors

- See Special Considerations for the Use of Small-Molecule Inhibitors (Ibrutinib, Idelalisib, and Venetoclax) (CSLL-F).

Vaccination

- Avoid all live vaccines, including Zoster
- Annual influenza vaccine[b] (live attenuated influenza vaccine should be avoided)
- Pneumococcal vaccine every 5 years

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

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

First-line therapy

- **Frail patient with significant comorbidity (not able to tolerate purine analogs)**
  - **Preferred regimens**
    - ◊ **Chlorambucil + obinutuzumab (category 1)**
    - ◊ **Ibrutinib[c] (category 1)**
    - ◊ **Chlorambucil + ofatumumab**
    - ◊ **Chlorambucil + rituximab**
  - **Other recommended regimens**
    - ◊ **High-dose methylprednisolone (HDMP) + rituximab (category 2B)**
    - ◊ **Obinutuzumab (category 2B)**
    - ◊ **Chlorambucil (category 3)**
    - ◊ **Rituximab (category 3)**

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

See monoclonal antibody and viral reactivation (See CSLL-C)

First-line therapy

- **Age ≥65 y and younger patients with significant comorbidities**
  - **Preferred regimens**
    - ◊ **Chlorambucil + obinutuzumab (category 1)**
    - ◊ **Ibrutinib[c] (category 1)**
    - ◊ **Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) ± CD20 monoclonal antibody[d]**
    - ◊ **Chlorambucil + ofatumumab**
    - ◊ **Chlorambucil + rituximab**
  - **Other recommended regimens**
    - ◊ **HDMP + rituximab (category 2B)**
    - ◊ **Obinutuzumab (category 2B)**
    - ◊ **Chlorambucil (category 3)**
    - ◊ **Rituximab (category 3)**

Post First-line Maintenance Therapy

- **Other recommended regimen**
  - **Consider lenalidomide for high-risk patients (blood MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated IGHV)[e] after first-line therapy**

First-line therapy

- **Age <65 y without significant comorbidities**
  - **Preferred regimens**
    - ◊ **FCR[f] (fludarabine,[g] cyclophosphamide, rituximab[h]) (category 1)[d]**
    - ◊ **Bendamustine ± CD20 monoclonal antibody[d]**
    - ◊ **Ibrutinib[c]**
  - **Other recommended regimens**
    - ◊ **FR[f] (fludarabine,[g] rituximab)[i]**
    - ◊ **HDMP + rituximab (category 2B)**
    - ◊ **PCR (pentostatin, cyclophosphamide, rituximab) (category 3)**

See Suggested Regimens for Relapsed/Refractory Therapy for CLL/SLL without del(17p)/TP53 mutation (2 of 5)

See Suggested Regimens for CLL/SLL with del(17p) (3 of 5)

[a]See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b]See Supportive Care for Patients with CLL/SLL (CSLL-C).
[c]See Special Considerations for Use of Small-Molecule Inhibitors (CSLL-F).
[d]CD20 monoclonal antibodies include: rituximab, ofatumumab, or obinutuzumab. Data from the CLL10 study confirm the superiority of FCR over BR in younger patients. For patients >65 y, the outcome was similar for both regimens with less toxicity for BR. BR may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is associated with fewer myelosuppressive toxicities.
[e]Minimal residual disease (MRD) evaluation with a sensitivity of 10-4 according to the standardized ERIC method.
[f]Autoimmune hemolytic anemia (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.
[g]See Discussion for further information on oral fludarabine.
[h]Rituximab and hyaluronidase human injection for subcutaneous use may be used for CLL in combination with fludarabine and cyclophosphamide (FC) regimen after patients have received at least one full dose of a rituximab product by intravenous route.
[i]Not recommended for CLL with del(11q). Outcomes for CLL with del11q are better with chemoimmunotherapy containing an alkylating agent.

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

Relapsed/Refractory Therapy

- **Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities**
  - **Preferred regimens**
    - ◊ **Ibrutinib[c] (category 1)**
    - ◊ **Idelalisib + rituximab[c,j] (category 1)**
    - ◊ **Venetoclax[c,k] + rituximab (category 1)**
  - **Other recommended regimens**
    - ◊ **Acalabrutinib[c,l]**
    - ◊ **Alemtuzumab[n] ± rituximab**
    - ◊ **Chlorambucil + rituximab**
    - ◊ **Reduced-dose FCR[f,g,h]**
    - ◊ **HDMP + rituximab**
    - ◊ **Idelalisib[c]**
    - ◊ **Lenalidomide[m] ± rituximab**
    - ◊ **Obinutuzumab**
    - ◊ **Ofatumumab**
    - ◊ **Reduced-dose PCR**
    - ◊ **Venetoclax[c,k]**
    - ◊ **Dose-dense rituximab (category 2B)**
    - ◊ **Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated), rituximab ± ibrutinib[c] or idelalisib[c] (category 2B for BR and BR + ibrutinib; category 3 for BR + idelalisib)**

Relapsed/Refractory Therapy

- **Age <65 y without significant comorbidities**
  - **Preferred regimens**
    - ◊ **Ibrutinib[c] (category 1)**
    - ◊ **Idelalisib + rituximab[c,j] (category 1)**
    - ◊ **Venetoclax[c,k] + rituximab (category 1)**
  - **Other recommended regimens**
    - ◊ **Acalabrutinib[c,l]**
    - ◊ **Alemtuzumab[n] ± rituximab**
    - ◊ **Bendamustine + rituximab**
    - ◊ **FC + ofatumumab**
    - ◊ **FCR[f,g,h]**
    - ◊ **HDMP + rituximab**
    - ◊ **Idelalisib[c]**
    - ◊ **Lenalidomide[m] ± rituximab**
    - ◊ **Obinutuzumab**
    - ◊ **Ofatumumab**
    - ◊ **PCR**
    - ◊ **Venetoclax[c,k]**
    - ◊ **Bendamustine, rituximab + ibrutinib[c] (category 2B)**
    - ◊ **Bendamustine, rituximab + idelalisib[c] (category 2B)**

Post Second-line Maintenance Therapy
(for complete or partial response after relapsed or refractory therapy)

- **Other recommended regimens**
  - **Lenalidomide[e]**
  - **Ofatumumab (category 2B)**

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

See Suggested Regimens for CLL/SLL with del(17p) (3 of 5)

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[c] See Special Considerations for Use of Small-Molecule Inhibitors (CSLL-F).
[e] Minimal residual disease (MRD) evaluation with a sensitivity of 10-4 according to the standardized ERIC method.
[f] Autoimmune hemolytic anemia (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.
[g] See Discussion for further information on oral fludarabine.
[h] Rituximab and hyaluronidase human injection for subcutaneous use may be used for CLL in combination with fludarabine and cyclophosphamide (FC) regimen after patients have received at least one full dose of a rituximab product by intravenous route.
[j] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[k] See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[l] Acalabrutinib should not be used for ibrutinib refractory CLL with BTK C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib without recurrence of these symptoms.
[m] 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 Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[n] While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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SUGGESTED TREATMENT REGIMENS[a,b]
CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by preference and category)

First-line Therapy
- **Preferred regimen**
  - **Ibrutinib[c]**
- **Other recommended regimens**
  - **Alemtuzumab[n] ± rituximab**
  - **HDMP + rituximab**
  - **Obinutuzumab**

Post First-line Maintenance Therapy
- **Other recommended regimen**
  - **Consider lenalidomide for high-risk patients (blood MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated IGHV or del(17p)/TP53 mutation)[e] after first-line therapy (category 3)**

Relapsed/Refractory Therapy
- **Preferred regimens**
  - **Ibrutinib[c] (category 1)**
  - **Venetoclax[c,k] + rituximab (category 1)**
  - **Idelalisib + rituximab[c,j]**
  - **Venetoclax[c,k]**
- **Other recommended regimens**
  - **Acalabrutinib[c,l]**
  - **Alemtuzumab[n] ± rituximab**
  - **HDMP + rituximab**
  - **Idelalisib[c]**
  - **Lenalidomide[m] ± rituximab**
  - **Ofatumumab[o]**

Post Second-line Maintenance Therapy
(for complete or partial response after relapsed or refractory therapy)
- **Other recommended regimens**
  - **Lenalidomide[e]**
  - **Ofatumumab (category 2B)**

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

See monoclonal antibody and viral reactivation (See CSLL-C)

See Suggested Regimens for CLL/SLL without del(17p) (1 of 5)

[a]See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b]See Supportive Care for Patients with CLL/SLL (CSLL-C).
[c]See Special Considerations for Use of Small-Molecule Inhibitors (CSLL-F).
[e]Minimal residual disease (MRD) evaluation with a sensitivity of 10^{-4} according to the standardized ERIC method.
[j]Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[k]See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[l]Acalabrutinib should not be used for ibrutinib refractory CLL with BTK C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib without recurrence of these symptoms.
[m]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 Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[n]While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.
[o]This is not effective in patients with lymph nodes >5 cm.

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SUGGESTED TREATMENT REGIMENS
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Fludarabine + rituximab

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Continued

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SUGGESTED TREATMENT REGIMENS
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Ibrutinib, bendamustine, rituximab
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Idelalisib, bendamustine, rituximab
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Venetoclax ± rituximab
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RESPONSE DEFINITION AFTER TREATMENT FOR CLL/SLL[a,b]

Parameter	CR	PR	PR-L[d]	PD
Group A Lymphadenopathy†	None >1.5 cm	Decrease ≥50%	Decrease ≥50%	Increase ≥50%
Hepatomegaly	None	Decrease ≥50%	Decrease ≥50%	Increase ≥50%
Splenomegaly[c]	None	Decrease ≥50%	Decrease ≥50%	Increase ≥50%
Marrow‡	Normocellular, <30% lymphocytes, no B-lymphoid nodules; hypocellular marrow defines CR with incomplete marrow recovery (CRi)	50% reduction in marrow infiltrate, or B-lymphoid nodules	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Blood lymphocytes	<4000/μ/L	Decrease ≥50% over baseline	Increase or decrease <50% over baseline	Increase ≥50% over baseline[b]
Group B Platelet count without growth factors	>100,000/μ/L	>100,000/μ/L or increase ≥50% over baseline	>100,000/μ/L or increase ≥50% over baseline	Decrease ≥50% over baseline secondary to CLL
Hemoglobin without transfusions or growth factors	>11.0 g/dL	>11 g/dL or increase ≥50% over baseline	>11 g/dL or increase ≥50% over baseline	Decrease of >2 g/dL from baseline secondary to CLL
Neutrophils without growth factors‡	>1500/μ/L	>1500/μ/L or >50% improvement over baseline	>1500/μ/L or >50% improvement over baseline	

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, and patients have to lack disease-related constitutional symptoms.
Partial remission (PR): requires 1) having two of the group A criteria if 2 or more are present. Patients with one group A criterion (excluding bone marrow) are also considered evaluable for response; 2) one group B criterion whether or not normal from baseline prior to starting therapy.
Stable disease is absence of progressive disease (PD) and failure to achieve at least a PR.
PD: appearance of any new lesions; at least one of the above criteria of group A or group B has to be met.
†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).
‡These parameters are irrelevant for some response categories.

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[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]MRD-negative status in peripheral blood (PB) correlates with better PFS. Analysis from GCLLSG study indicates that if PB is MRD negative, residual splenomegaly has no clinical significance. Kovacs G, Boettcher S, Bahlo J, et al. Blood 2014;124:Abstract 23.
[d]Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2822.

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

ACALABRUTINIB

- Dosage: The recommended dose of acalabrutinib is 100 mg PO BID administered in 28-day cycles until progression of disease or development of side effects that require dose reduction or cessation of therapy. Early lymphocytosis is expected with acalabrutinib therapy and is not considered a sign of progression but rather an on-target effect of the drug. Additionally, patients who have been on acalabrutinib and then have their medication held can have a small node or lymphocytosis flare. Re-initiation of therapy generally is effective in this setting. Administration of proton pump inhibitors should be avoided if possible as this influences absorption of acalabrutinib.
- Toxicity:
  - No ≥Grade 3 bleeding events occurred in the initial trial and subsequent studies have had a low frequency of this. Grade ≥3 hypertension and atrial fibrillation were observed in 3% and 2% of patients, respectively. Monitor for atrial fibrillation/ hypertension and manage as appropriate.
  - Acalabrutinib may increase the risk of hemorrhage in patients receiving anti-platelet or anticoagulant therapies. Trials with acalabrutinib excluded patients receiving warfarin. Patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3 days pre-and post-surgery depending on the type of surgery and risk of bleeding.
  - Headaches are commonly observed with acalabrutinib early in therapy and typically resolve with time over 1-2 months of therapy. These generally can be managed with analgesics such as acetaminophen and caffeine supplements.
- Acalabrutinib has no activity against CLL cells with BTK C481S mutations and should not be administered to patients with ibrutinib refractory disease who have this mutation present in their tumor cells.

IBRUTINIB

- Dosage
  - The recommended dose of ibrutinib is 420 mg PO daily, continuous and should be continued until time of progression.
- Lymphocytosis
  - Upon initiation of ibrutinib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and may persist for several weeks on treatment.
- Grade >2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded patients on concurrent warfarin. Ibrutinib should be held 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure. Ibrutinib should not be given concomitantly with warfarin.
- New-onset atrial fibrillation was reported in 6%–9%, associated with ibrutinib administration.
  - Consider non-warfarin anticoagulation
  - Monitor carefully
  - If uncontrolled, consider switching to alternate therapy
  - If switching to venetoclax, assess risk for TLS
- Hypertension associated with ibrutinib has been uncommonly reported as a basis for discontinuation and should be mananged with anti-hypertensives as appropriate. Ibrutinib should only be discontinued for uncontrollable hypertension.
- At time of disease progression on ibrutinib, transition to next therapy as soon as possible upon stopping ibrutinib since progression may accelerate when ibrutinib is stopped. Treatment-free interval should be as short as possible.
- Testing for *BTK* and *PLCG2* mutations may be useful in patients receiving ibrutinib and suspected of having progression. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment.

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

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

IDELALISIB

- **Dosage**
  - **The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.**
- **Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.**
  - **Hepatotoxicity: Monitor hepatic function prior to and during treatment. Interrupt if ALT/AST >5 x ULN (upper limit of normal) and when resolved may resume at a reduced dose (100 mg PO twice daily).**
  - **Diarrhea or colitis: Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.**
  - **Pneumonitis: Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.**
  - **Intestinal perforation: Discontinue idelalisib if intestinal perforation is suspected.**
- **Lymphocytosis**
  - **Upon initiation of idelalisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of idelalisib therapy and may persist for several weeks on treatment.**
- **CMV reactivation: See CSLL-C.**
- **PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent.**

VENETOCLAX

- **Dosage**
  - **The recommended dose of venetoclax is 400 mg PO daily until disease progression or unacceptable toxicity.**
  - **Initiate venetoclax at 20 mg for one week and gradually escalate to target dose of 400 mg PO daily over 5 weeks to reduce the risk of tumor lysis syndrome. See CSLL-G for recommended TLS prophylaxis and monitoring based on tumor burden.**
  - **Consider re-initiating at a lower dose then continue with dose escalation, in patients who have treatment interruption for >1 week during escalation.**
- **Initiation and accelerated escalation of venetoclax (20 mg to 400 mg over 3-weeks) with close inpatient TLS monitoring can be done in the subgroup of patients with high tumor burden and where there is concern for rapid disease progression on or following BTK-inhibitor therapy. For accelerated escalation, venetoclax is administered at 20 mg on Week (W)1/Day (D)1, 50 mg on W1/D2-3, 100 mg on W1/D4-7 (all inpatient), then outpatient unless concern for TLS, 200 mg on W2/D1-7, and 400 mg on W3/D1-continuous.[2] Additionally, continued BTK-inhibition concurrent with initiation and escalation of venetoclax with discontinuation of BTK-inhibitor when up to the venetoclax 400 mg daily dose can be considered. These agents can be given together safely.**
- **Consider the use of neutrophil growth factors according to standard guidelines. Dose reduction may be necessary for persistent neutropenia and limited bone marrow involvement with CLL.**

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

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

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

Co-administration with CYP3A Inhibitors and Inducers

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

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

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

- **Venetoclax**
  - **Avoid concomitant use of strong CYP3A inhibitors or inducers.**

Co-administration with Gastric Acid Reducing Agents

- **Acalabrutinib**
  - **Avoid co-administration with proton pump inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids.**

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

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

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

Tumor Burden[b]	Prophylaxis[c]	Blood Chemistry Monitoring[e,f]
Low All lymph nodes <5 cm AND Absolute lymphocyte count (ALC) <25 x10^9/L	• Oral hydration (1.5–2 L) • Allopurinol[d]	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium Any lymph node 5 cm to <10 cm OR ALC ≥25 x10^9/L	• Oral hydration (1.5–2 L) and consider additional intravenous hydration • Allopurinol	Outpatient • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for patients with CrCl <80 mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High Any lymph node ≥10 cm OR ALC ≥25 x10^9/L AND any lymph node ≥5 cm	• 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 to 8 hours, 24 hours

[a]Prescribing information for venetoclax. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf.
[b]Lymph node size should be evaluated by chest/abdominal/pelvic CT scan with contrast.
[c]Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[d]Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
[e]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[f]For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

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DIAGNOSIS

ESSENTIAL:

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

→ See Workup (HT-2)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- **FISH to detect +12; del(11q); del(13q); del(17p)**
- **CpG-stimulated metaphase karyotype for complex karyotype**
- **Molecular analysis to detect IGHV mutation status of CLL and transformed tissue[e]**
- **TP53 sequencing**

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

[b]Proliferation centers in CLL may express cMYC and/or CyclinD1. This does not change the diagnosis.

[c] First, "CLL with expanded proliferation centers" or "accelerated CLL" may be diagnosed in cases where proliferation centers in CLL are expanded or fuse together (>20x field or 0.95 mm^2) AND show Ki67 proliferative rate >40% or >2.4 mitoses/proliferation center. Second, progression to "CLL with increased prolymphocytes" or "CLL/PLL" may occur when there are increased prolymphocytes in the blood (>10%–<55%). Neither of these findings should be considered a transformation event, but rather as progression of CLL. B-PLL should be reserved for the diagnosis of de novo leukemias that are not associated with CLL.

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

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

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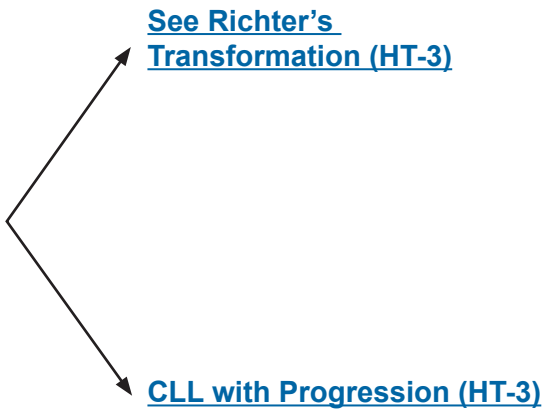
WORKUP

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

USEFUL IN SELECTED CASES:
- Unilateral bone marrow aspirate and biopsy
- MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated
- Hepatitis B testing[f]
- Pregnancy testing in women of child-bearing age
- Human leucocyte antigen (HLA) typing



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

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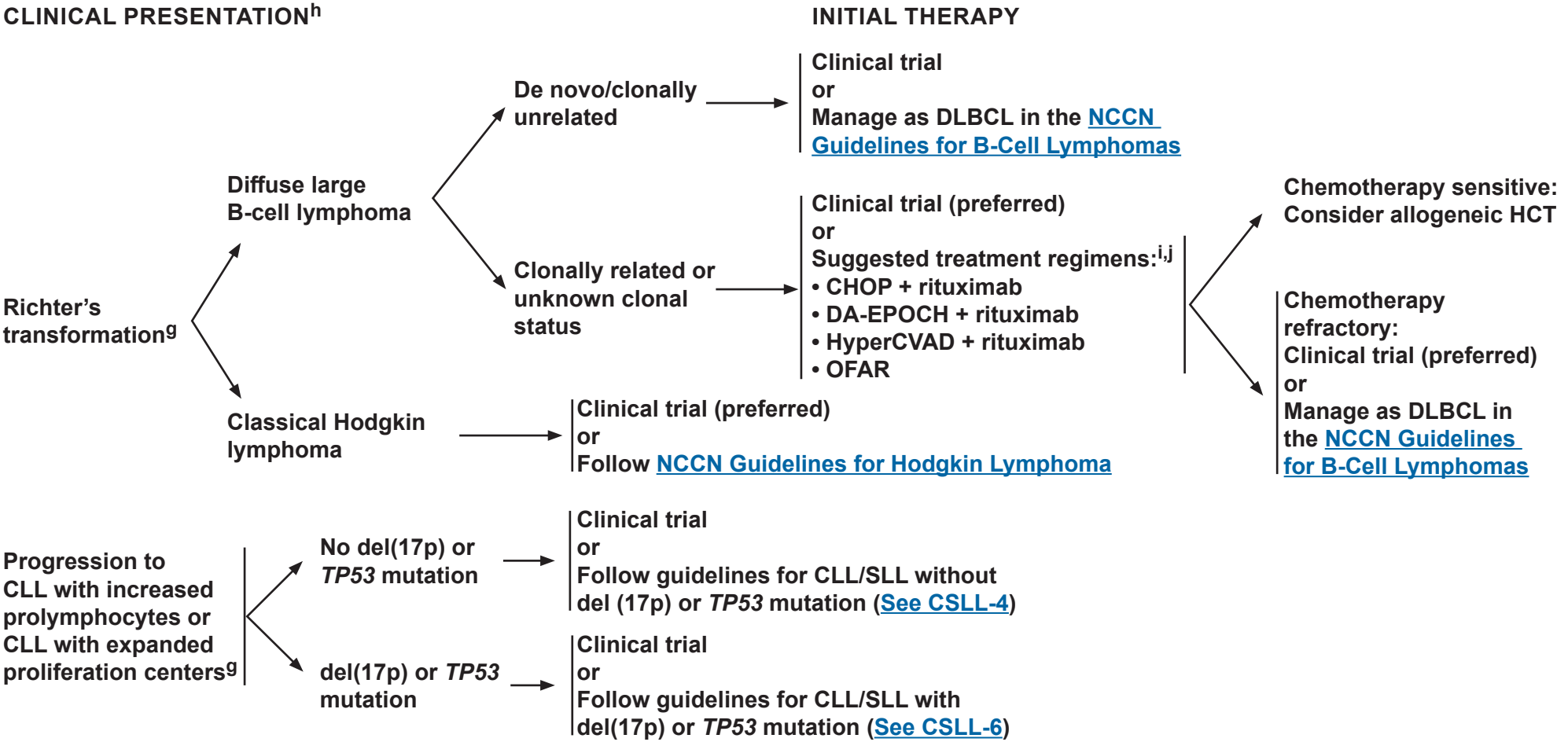

[g]"Accelerated CLL," "CLL with expanded proliferation centers," and "CLL-PLL or CLL with increased prolymphocytes" (defined on HT-1) are not considered Richter's transformation, but are associated with more aggressive disease and poorer outcome {Gine E et al, Haematologica Sep 2010, 95 (9) 1526-1533; Ciccone M et al, Leukemia (2012) 26, 499–508; WHO 2016}. Optimal management for these cases has not been established.

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

[i]Richter's transformation to DLBCL (clonally related or unknown clonal status) is generally managed with treatment regimens recommended for DLBCL. However, these regimens typically result in poor responses.

[j]See references for regimens HT-A.

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SUGGESTED TREATMENT REGIMENS (REFERENCES)

DA-EPOCH-R

Rogers K, Salem G, Stephens D, et al. A single-institution retrospective cohort study of patients treated with R-EPOCH for Richter's transformation of chronic lymphocytic leukemia [abstract]. Blood 2015;126:Abstract 2951.

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

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

RCHOP

Tsimberidou AM, O'Brien S, 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.

Transplant

Cwynarski K, van Biezen A, de Wreede L, et al. Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): A retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2012;30:2211-2217.

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Discussion

NCCN Categories of Evidence and Consensus

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

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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Overview

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) comprises approximately 7% of newly diagnosed cases of non-Hodgkin's lymphomas (NHL).[1] CLL remains the most prevalent adult leukemia in Western countries, but is considered rare in regions such as East Asia. In 2018, an estimated 20,940 people will be diagnosed with CLL in the United States, and an estimated 4,510 people will die from the disease.[2] Morphologically, the leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or prolymphocytes.[3] CLL and SLL are different manifestations of the same disease and are managed in much the same way.[4] CLL/SLL is characterized by a progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. The major difference is that in CLL, a significant number of the abnormal lymphocytes are found in blood in addition to bone marrow and lymphoid tissue, while in SLL there are few if any abnormal lymphocytes circulating in blood, and the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for CLL/SLL, an electronic search of the PubMed database was performed to obtain key literature in "Chronic Lymphocytic Leukemia" published between May 2016 and April 2017 using the following search terms: chronic lymphocytic leukemia, Richter syndrome, and Richter's transformation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[5]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 117 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Staging

The Lugano Modification of Ann Arbor Staging System is used for SLL.[6] The Rai and Binet systems are the two staging systems currently used worldwide in the evaluation of patients with CLL both in the routine practice and clinical trial settings.[7,8] Both rely solely on physical examination (presence of lymph node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden. The modified Rai classification stratifies patients into 3 risk groups.[7] Survival of patients with low-risk disease (Rai stage 0; median survival 150 months) is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease (Rai stage I-II; median survival 71–101 months) have shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than one year. Patients with high-risk features (Rai stage III-IV; median survival 19 months) have a poor prognosis.

The Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets and, similar to the Rai staging system, provides meaningful correlation with clinical outcome.[8]

Response Criteria

The response criteria set forth in the 1996 National Cancer Institute-sponsored Working Group (NCI-WG) guidelines are used in most clinical trials.[9] In 2008, these response criteria were revised by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) to reflect recent advances in our understanding of newer prognostic markers, diagnostic parameters, and treatments.[3] In particular, the 2008 IWCLL guidelines provide further recommendations for the evaluations and response assessments appropriate for the general clinical practice setting versus for clinical trials.[3]

In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. All of the following criteria must be met for a complete response (CR), at least 2 months after treatment completion: peripheral blood lymphocyte counts <4 $\times 10^9$/L; absence of lymphadenopathy (ie, palpable nodes must be ≤1.5 cm in diameter); absence of splenomegaly or hepatomegaly; absence of constitutional symptoms (ie, weight loss, significant fatigue, fevers, night sweats); and normalization of blood counts without growth factor support (ie, neutrophils >1.5 $\times 10^9$/L, platelets >100 $\times 10^9$/L, hemoglobin >11 g/dL).[3] Confirmation of CR requires bone marrow evaluation with aspirate and core biopsy, demonstrating <30% lymphocytes, with no B lymphoid nodules. At least 2 of the following criteria must be met for at least 2 months duration for a partial response (PR): at least 50% reductions in peripheral blood lymphocyte counts (from baseline); lymphadenopathy (based on sum of the products of multiple affected nodes); hepatomegaly; and/or splenomegaly. In addition, at least 1 of the blood counts should be normalized or increase by ≥50% from baseline, for at least 2 months duration. Progressive disease comprises any of the following: at least 50% increase from baseline in lymphocyte counts, lymphadenopathy, hepatomegaly, or splenomegaly; appearance of any new lesions; or occurrence of cytopenias attributable to disease (ie, ≥50% decrease from baseline in platelet count, >2 g/dL decrease from baseline in hemoglobin levels).[3] Patients who do not have progressive disease but do not meet the criteria for a CR or PR are considered to have stable disease. Relapse is defined as evidence of disease progression after a period of 6 months or more following an initial CR or PR. Refractory disease is defined as failure to achieve a response or having disease progression within 6 months of the last treatment.[3]

CT scans are desirable in clinical trials for evaluations of adenopathy and organ involvement and select patients outside of trials. In addition, a bone marrow evaluation should be conducted to confirm a CR (<30% lymphocytes, normocellular morphology, absence of lymphoid nodules) if all other criteria for clinical CR (as defined above) are met. Patients who fulfill the criteria for a CR (including evaluation of the bone marrow), but present with persistent cytopenias due to treatment-related toxicities, should be considered as having achieved a CR with incomplete marrow recovery.[3]

The IWCLL response criteria were recently revised to more precisely predict the outcome for patients with CLL treated with immunomodulating agents and small molecule kinase inhibitors.[10]

Treatment with immunomodulating agents such as lenalidomide can result in a tumor flare reaction characterized by painful enlargement of

lymph nodes, lymphocytosis, rash, and bone pain. Tumor flare reaction was correlated with clinical response in patients with CLL treated with lenalidomide.[11]

The use of ibrutinib, acalabrutinib and idelalisib results in an initial transient increase in lymphocytosis due to redistribution or release of leukemic cells from the lymph node compartment to the peripheral blood.[12-14] In the majority of patients treated with ibrutinib, lymphocytosis resolves within 8 months, but in a subgroup of patients lymphocytosis lasts for more than 12 months. Prolonged lymphocytosis following ibrutinib treatment was reported to represent the persistence of a quiescent clone and does not predict a subgroup of patients likely to progress early.[12] Considering these findings, for patients receiving of ibrutinib, acalabrutinib and idelalisib, the revised response criteria proposed by Cheson et al allow for a new response category, "PR with lymphocytosis," to include those with a clinical response (reduction in lymph nodes and splenomegaly) with persistent lymphocytosis (in the absence of other indicators of progressive disease).[10]

Minimal residual disease (MRD) negativity determined in the peripheral blood after the end of treatment is emerging as an important predictor of treatment efficacy.[15,16] In the combined analysis of two randomized phase III studies of the German CLL Study Group (GCLLSG) (CLL8 and CLL10), among patients who achieved CR and PR, progression-free survival (PFS) was longer for those with MRD-negative CR and MRD-negative PR (61 months and 54 months, respectively) than those with MRD-positive CR and MRD-positive PR (35 months and 21 months, respectively).[15] The persistence of post-treatment splenomegaly as a sole abnormality in MRD-negative patients did not have a negative impact on PFS. MRD-negativity after end of treatment with first-line fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy also correlated with PFS.[16] These results support the use of MRD for response evaluation.

Prognostic Factors

Immunoglobulin heavy-chain variable (*IGHV)* region gene mutational status, cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) such as del(13q), del(11q), or del(17p), flow cytometry-based prognostic markers (CD38, CD49d, and ZAP-70), and serum markers (thymidine kinase and beta-2 microglobulin) may provide useful prognostic information beyond clinical staging. The survival estimates for traditional clinical and laboratory prognostic factors as well as the newer prognostic factors were generated in an era of chemotherapy or chemoimmunotherapy. Newer small molecule inhibitor-based therapy has significantly improved survival outcomes, including patients with high-risk disease, and there is limited follow-up with these treatments. Therefore, caution should be taken in interpreting these survival data.

IGHV mutational status is an important predictor of survival outcomes. Unmutated *IGHV* (≥98% homology with germline gene sequence) is associated with poor prognosis and significantly decreased survival compared with mutated *IGHV*, irrespective of the stage of the disease.[17,18] In addition, *VH3-21* gene usage was associated with poor outcomes regardless of the mutation status (as defined by percent homology with germline sequence).[19] Unmutated *IGHV* or the use of *VH3-21* was shown to be an independent predictor of shorter treatment-free interval and/or survival outcomes, even when high-risk genomic abnormalities were included in the multivariable regression models.[20-23] *IGHV* mutation testing is recommended based on reproducibility and ready availability.

Cytogenetic abnormalities that can be detected by FISH are present in more than 80% of patients with previously untreated CLL. Del(13q) (55%), del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%) are the most common abnormalities.[24] Del(13q) as a sole abnormality is associated with favorable prognosis and the longest median survival (133 months). Del(11q) is often associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 months).[24] The addition of an alkylating agent to fludarabine-based chemoimmunotherapy may help to overcome the adverse prognostic significance of del(11q) in patients with previously untreated CLL.[23,25] Del(17p), which reflects the loss of the *TP53* gene and is frequently associated with mutations in the remaining *TP53* allele, is associated with worst outcomes, with short treatment-free interval, short median survival (32 months), and poor response to chemotherapy.[24] Del(17p) is more frequently observed in patients with previously treated CLL, suggesting that acquisition and/or expansion of CLL clones with del(17p) may occur during the course of treatment.[26] Abnormalities of *TP53* can be observed in the absence of del(17p) and *TP53* mutations have been identified as predictors of poor survival and resistance to fludarabine-based regimens, independent of 17p chromosome status.[27-29]

The impact of these cytogenetic abnormalities on clinical outcome has been evaluated in large prospective randomized studies.[23,30,31] In the CLL4 trial, which compared chlorambucil vs. fludarabine vs. fludarabine and cyclophosphamide (FC) as first-line therapy, *TP53* loss was found to be the strongest predictor of poor outcomes.[23] Among the subgroup of patients without *TP53* loss, unmutated *IGHV* (or *VH3-21* usage) and elevated beta-2 microglobulin (>4 mg/L) were significant independent predictors for both PFS and overall survival (OS) outcomes.[23] In addition, del(11q) and treatment allocation were independent predictors for PFS and age was an independent predictor for OS. In the long-term follow-up from the CALGB 9712 study that evaluated first-line therapy with concurrent vs. sequential fludarabine and rituximab, unmutated *IGHV* was a significant independent predictor for shorter PFS and OS and poor-risk cytogenetic abnormalities, del(17p) or del(11q), were independent predictors for shorter survival.[30] In the phase III randomized CLL8 study that compared FC versus FCR as first-line therapy, the presence of *TP53* mutation, del(17p), and unmutated *IGHV* were the strongest predictors of shorter PFS and OS.[31] The median PFS was significantly longer in patients with mutated *IGHV* treated with FCR than those treated with FC (not reached for FCR vs. 42 months for FC; $P < .001$), and the 5-year OS rates were 86% and 80%, respectively. Among patients with mutated *IGHV*, improvement in survival was seen across all cytogenetic subgroups except for those with del(17p).

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.[23,32] In the CLL4 trial, the presence of del(17p) in ≥10% or more cells was the strongest predictor of poor outcomes.[23] Patients with del(17p) in ≥10% cells had a response rate of 29% and a median survival of <6 months.[23] However, outcomes were similar between patient subgroups with del(17p) in 5% to 10% of cells and the subgroup with del(17p) in <5% of cells. Patients with del(17p) in 10% to 20% of cells had outcomes similar to patients with del(17p) in >20% of cells. In a more recent report that assessed the impact of cytogenetic abnormalities detected by FISH on clinical outcome in a cohort of 1585 patients with CLL, patients with del(17p) in ≤20% of cells were more likely to have mutated *IGHV*, longer median time to first treatment, and longer OS from the date of the first FISH study.[33]

Complex karyotype (≥3 unrelated chromosomal abnormalities in more than one cell on CpG-stimulated karyotype of CLL cells) is emerging as a stronger predictor of poor clinical outcomes than del(17p) in patients with CLL treated with ibrutinib-based regimens.[34-38] Among patients with relapsed/refractory CLL treated with ibrutinib-based regimens, in a multivariate analysis, only complex karyotype was significantly associated with inferior event-free survival (EFS; $P = .006$), whereas fludarabine-refractory CLL ($P = .005$) and complex karyotype ($P = .008$) were independently associated with inferior OS.[35] In another analysis of 308 patients treated with ibrutinib on four sequential clinical trials, in a multivariate analysis, complex karyotype at baseline, presence of del(17p), and age <65 years were all independently associated with a risk for CLL progression.[38] In patients ≥65 years without complex karyotype or del(17p), the estimated cumulative incidence of CLL progression at 4 years was 2% compared to 44% in patients <65 years with complex karyotype and del(17p).

Recent reports suggest that resistance to ibrutinib is associated with mutations in *BTK* and *PLCG2* genes.[38,39] Among patients with relapsed CLL after treatment with ibrutinib, acquired mutations in *BTK* and/or *PLCG2* were found in 85% of patients and these mutations were detected at an estimated median of 9 months before relapse.[38] The reported variant allele frequencies (VAF) are variable with often low VAF associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance. *BTK* and/or *PLCG2* mutations have also been detected in patients with progressive CLL during ibrutinib therapy up to 15 months before the manifestation of clinical progression.[39] These findings suggest that testing for these mutations may be helpful to confirm ibrutinib resistance. Testing for mutations as screening for resistance is not currently recommended.

Recurrent mutations in *NOTCH1*, *SF3B1*, and *BIRC3* genes with prognostic implications have been identified in approximately 4% to 15% of patients with newly diagnosed CLL and the incidences are much higher (15%–25%) in patients with CLL refractory to fludarabine.[40-45] *NOTCH1* mutation is also independently associated with Richter's transformation.[46,47] Data from prospective clinical trials have also confirmed that *NOTCH1* and *SF3B1* mutations are predictors of shorter survival in patients with newly diagnosed as well as relapsed or refractory CLL.[48-50] In the German CLL2H study, *NOTCH1* mutations were associated with longer PFS compared with wild-type cases, and *SF3B1* mutations had no impact on PFS or OS.[49] In a multivariable analysis, *NOTCH1* mutation was found to be an independent predictor of favorable PFS in patients with fludarabine-refractory CLL. In the UK CLL4 trial, both *NOTCH1* and *SF3B1* mutations were associated with shorter OS, and both retained independent prognostic significance for survival outcomes in a multivariable analysis.[50] In the CLL8 trial, *TP53* and *SF3B1* mutations were the strongest prognostic markers in patients receiving current standard first-line therapy, whereas *NOTCH1* mutation was identified as a predictive marker for decreased benefit from the addition of rituximab to FC.[29] Collectively, the above studies suggest that the prognostic significance of these mutations may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated. Although these prognostic factors may provide useful prognostic information, the impact of these mutations relative to treatment with newer targeted therapies is uncertain. Treatment initiation or selection of treatment options should not be driven by these factors.

Among the flow cytometry-based prognostic parameters (CD38, CD49d and ZAP-70), CD49d appears to be the strongest predictor of OS and treatment-free survival.[51-54] Increased expression of CD49d (≥30%) is

associated with progressive disease (advanced clinical stage, high serum lactate dehydrogenase, or beta-2-microglobulin levels) and aggressive disease biology (increased ZAP70 or CD38, unmutated *IGHV*, trisomy 12, and lack of isolated del(13q)).[51,54] Expression of CD38 (≥7%)[17,21,23,55-57] and/or ZAP-70 (≥20%) are associated with shorter PFS and OS outcomes.[58-63] Both CD38 and ZAP-70 positivity correlate with unmutated *IGHV*, and were suggested as potential surrogate markers for *IGHV* mutational status.[17,58,59] However, discordant results between CD38 positivity and *IGHV* mutational status were observed in up to 28% of patients in one study; moreover, CD38 expression levels may vary over the course of the disease.[64] Similarly, discordant results between ZAP-70 positivity and *IGHV* mutational status were reported in 20% to 25% of cases.[23,61] In addition, it was suggested that ZAP-70 positivity may be a stronger predictor of outcomes (eg, time to first treatment) than *IGHV* mutational status or CD38 levels.[61-63]
ZAP-70 methylation analysis (which is closely associated with ZAP-70 expression and *IGHV* mutational status) was also reported to be a useful prognostic test for patients with CLL.[65-67] CD49d, CD38, and ZAP-70 expressions can be determined using immunohistochemistry (IHC) or flow cytometry. However, standardization and reproducibility of these markers across laboratories remains a challenge. Evaluation of CD49d, CD38, and ZAP-70 is not recommended outside the context of clinical trials.

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 regimens.[68,69] In a multivariable analysis that included baseline beta-2 microglobulin, stage of disease, fludarabine-refractory disease, and del(17p), failure to achieve normalized beta-2 microglobulin at 6 months of treatment was associated with inferior PFS for patients on ibrutinib-based treatment.[69] One of the advantages of beta-2 microglobulin is that it is readily measured by standard laboratory evaluation of blood samples. However, it is influenced in a CLL disease-independent manner by renal dysfunction.

Several prognostic models incorporating multiple clinical and prognostic markers have been developed for the risk stratification.[70-76]

A prognostic nomogram and a more simplified prognostic index were developed using age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes to help stratify patients with untreated CLL into 3 different risk groups (low, intermediate, and high).[70] The estimated median survival times were not reached,10 years, and 5 years, respectively, for the 3 risk groups. The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.[70] Several studies have independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in patients with untreated CLL, including those with early-stage (Rai stage 0) disease.[71,72]

Another multivariable model incorporating traditional and newer prognostic factors such as FISH cytogenetics, *IGHV* mutational status, and ZAP-70 expression was developed to estimate the probability of treatment (at 2 and 4 years) and time to first treatment.[73] Increased size of cervical lymph nodes, 3 involved nodal sites, del(17p) or del(11q), unmutated *IGHV* status, and elevated serum LDH levels were identified as independent predictors of shorter time to first treatment.[73] This prognostic model may help to identify newly

diagnosed patients at high risk for disease progression who may require earlier intervention.

Integrated CLL Scoring System (ICSS) is a prognostic scoring system that stratifies patients into 3 risk groups (low, intermediate, and high) based on the cytogenetic abnormalities by FISH, *IGHV* mutational status, and CD38 expression.[75] International prognostic index for CLL (CLL-IPI) stratifies patients into 4 risk groups (low, intermediate, high, and very high) based on *TP53* and *IGHV* mutational status, serum beta-2 microglobulin concentration, clinical stage, and age.[76] The 5-year OS rates were significantly different between these risk groups (93%, 79%, 63%, and 23%, respectively).

An integrated prognostic model including *NOTCH1*, *SF3B1*, and *BIRC3* mutations along with the cytogenetic abnormalities identified by FISH has been proposed to classify patients into 4 distinct prognostic subgroups: high-risk (*TP53* and/or *BIRC3* abnormalities); intermediate-risk (*NOTCH1* and/or *SF3B1* mutations and/or del(11q)); low-risk (trisomy 12 and wild-type for all genetic lesions), and very low-risk (del(13q) only).[74] The 10-year survival rates for the 4 subgroups were 29%, 37%, 57%, and 69%, respectively.

Diagnosis

The diagnosis of CLL requires the presence of at least 5000 clonal B-cells/mcL (5 x 10^9/L) in the peripheral blood and the clonality of B-cells should be confirmed by flow cytometry.[3] The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with less than 5000 B-lymphocytes/mcL (5 x 10^9/L) in the peripheral blood.[3] B-cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when effacement of the lymph node architecture is observed in biopsy samples.

The presence of fewer B-cells in the absence of palpable lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder is defined as monoclonal B-cell lymphocytosis (MBL). MBL is a relatively recent diagnostic category describing individuals who present with an abnormal B-cell population with immunophenotype of CLL but do not meet the diagnostic criteria for CLL.[77] The estimated rate of progression of MBL to CLL was 1.1% per year. Favorable molecular lesions, mutated *IGHV* and del(13q), or normal cytogenetics are commonly seen in individuals with MBL.[77]

The guidelines now include an initial stratification between CLL/SLL and MBL. Observation is recommended for all individuals with MBL.

Flow cytometry of peripheral blood is adequate for the diagnosis of CLL, and bone marrow biopsy is generally not required. A diagnosis of SLL should ideally be confirmed by the evaluation of lymph node biopsy. The typical immunophenotype for CLL/SLL is CD5+, CD10-, CD19+, and CD20 dim, surface immunoglobulin dim, CD23+, CD43 +/-, and cyclin D1-. Cell surface markers for flow cytometric studies should include kappa/lambda, CD19, CD20, CD5, CD23, and CD10. Paraffin-section IHC on excisional or incisional lymph node biopsy materials can be performed if a diagnosis is not established by flow cytometry. The recommended IHC panel includes CD3, CD5, CD10, CD20, CD23, and cyclin D1. These can be useful, particularly for diagnosing CLL/SLL type without circulating leukemic cells.

Distinguishing CLL/SLL from mantle cell lymphoma (MCL) is essential, as they are both CD5+ B-cell tumors. Though CD23 is often helpful, absence of cyclin D1 expression is critical in this differentiation of tumor types. CD200 and LEF1 are also useful markers to distinguish CLL from MCL.[78-81] Evaluation of cyclin D1 (flow cytometry or IHC) or FISH

analysis for t(11;14), flow cytometry evaluation of CD200, and IHC for LEF1 may be helpful in the differential diagnosis of CLL.

FISH for the detection of del(11q), del(13q), trisomy 12, del(17p), stimulated metaphase karyotype, *TP53* sequencing, and molecular genetic analysis (by polymerase chain reaction [PCR] or sequencing) to detect *IGHV* mutation status can provide useful prognostic information and may guide selection of therapy. Expression of CD38, CD49d, and ZAP-70 expression by flow cytometry, methylation, or IHC have been proposed as surrogate markers for *IGHV*-mutation status. *IGHV* mutation status determination is preferred over these surrogate markers. Cytogenetic abnormalities can evolve over time; therefore, re-evaluation of FISH and karyotype is necessary to direct treatment options in patients with indications for treatment. CpG-stimulated karyotyping is useful to identify high-risk patients, particularly for treatment with ibrutinib.

Conventional metaphase cytogenetics is difficult in CLL as a result of the very low *in vitro* proliferative activity of the leukemic cells. Therefore, interphase cytogenetic analysis with 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.[82,83] A prospective study conducted by CLL Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens; moreover, the clonal abnormalities revealed by CpG-stimulated metaphase cytogenetics are consistent with that detected by interphase cytogenetic analysis with FISH and are reproducible among different cytogenetic laboratories.[83]

Workup

The workup for CLL/SLL is similar to the workup for other lymphoid neoplasms. Quantitative immunoglobulins may be informative in patients with recurrent infections. Measurement of beta-2 microglobulin may provide useful prognostic information.[70] Though classically the pattern of bone marrow involvement (diffuse vs. nodular) had prognostic significance, this is no longer a factor when one uses more reliable prognostic markers such as *IGHV* mutational status and cytogenetic abnormalities determined by FISH, all of which can be obtained by analysis of circulating lymphocytes. Thus, bone marrow biopsy is no longer considered a required part of the diagnostic evaluation of patients with suspected CLL, though it remains useful to evaluate the etiology of cytopenias.

CT scans may be useful to follow and monitor disease progression in patients with new symptoms when peripheral adenopathy is not present. For asymptomatic patients, serial CT scans are not recommended. For anemic patients, reticulocyte counts and a direct Coombs test should be performed to evaluate for the possibility of hemolysis and pure red cell aplasia (PRCA). PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.[84,85] Bone marrow biopsy ± aspirate could be useful in certain circumstances prior to initiation of treatment.

Localized SLL (Lugano stage I)

Locoregional radiation therapy (RT; 24–30 Gy) is an appropriate induction therapy for patients with symptomatic localized disease. In rare patients, RT may be contraindicated or may be a suboptimal therapy due to the presence of comorbidities or the potential for long-term toxicity. Patients with localized SLL that has progressed after

initial RT should be treated as described below for patients with SLL (Lugano stage II–IV).

SLL (Lugano stage II-IV) or CLL (Rai stages 0-IV)

Early-stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. In the absence of disease symptoms, a "watch and wait" approach is often appropriate for patients with stage II-IV SLL, low-risk CLL (Rai stage 0; Binet A), or intermediate-risk CLL (Rai stage I-II or Binet B) and treatment will be beneficial if they become symptomatic or show evidence of progressive disease.[3] Patients with advanced-stage or high-risk CLL (Rai stage III-IV or Binet C) with progressive cytopenia require treatment. Selected patients with mild, stable cytopenia may continue to be observed.

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; autoimmune anemia; or thrombocytopenia unresponsive to corticosteroids.[3] Absolute lymphocyte count alone is not an indication for treatment unless it is above 200 to 300 × 10^9/L or symptoms related to leukostasis occur.[3]

In patients with indications for initiating treatment, patient age, performance status or fitness, and the presence or absence of del(17p) or *TP53* mutation should then help to direct treatment options, as discussed below. Evaluation for *TP53* mutation status and cytogenetic abnormalities by FISH and stimulated karyotype are recommended prior to initiating treatment.

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

Prevention and management of disease-specific complications and treatment-related side effects are outlined under *Supportive Care*. Management of specific adverse events associated with novel targeted therapies are outlined under *Special Considerations for the Use of Small Molecule Inhibitors*.

Assessment of Functional Status and Comorbidity

CLL/SLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. Comorbidities are frequently present in older patients. In addition, organ function and bone marrow reserve also decline with advancing age. In a study that assessed the comorbidity burden and investigated its impact on treatment in 555 patients with untreated CLL enrolled in two GCLLSG trials, 26% of patients had comorbidities involving the metabolic/endocrine system, 21% of patients had comorbidities in the vascular system, and 12% of patients had cardiac comorbidities.[86] The presence of multiple comorbidities (≥2 comorbidities) was an independent predictor of clinical outcome independent of patients' age or disease stage.[86] The median OS (72 vs. 90 months; $P < .001$) and PFS (21 vs. 32 months; $P < .01$) were significantly shorter for patients with ≥2 comorbidities than for those with less than 2 comorbidities. In a multivariate analysis, after adjustment for other prognostic factors and treatment, comorbidity maintained independent prognostic value. These findings underscore the need to assess comorbidities, in addition to patient age and performance status, prior to treatment selection.

Cumulative Illness Rating Scale (CIRS), Charlson Comorbidity Index, and the NCI Comorbidity Index are some of the scoring systems that can be used to assess comorbidities in patients with CLL. CIRS in

combination with creatinine clearance (CrCl) was used by the GCLLSG to assess the overall fitness of patients enrolled in clinical trials.[86,87]

The age cutoff of 65 years is used in most of the clinical trials, including the studies conducted by the GCLLSG. In a retrospective analysis that evaluated the impact of age on the outcome after initial therapy with different chemoimmunotherapy and chemotherapy regimens in patients with CLL enrolled in CALGB trials, the benefit of fludarabine compared with chlorambucil decreased marginally with age, with estimated hazard ratios of 0.70, 0.76, and 0.81 at 65 years, 70 years, and 75 years, respectively.[88] The benefit of fludarabine relative to chlorambucil also decreased at an earlier age for OS than for PFS, with the estimated hazard ratios of 0.88, 1.01, and 1.15 at 65 years, 70 years, and 75 years, respectively. In addition, approximately 44% of patients >65 years have some degree of chronic kidney disease, which also increases the likelihood of toxicity associated with fludarabine-based regimens.[89] Based on these data, the panel decided to change the age cutoff from 70 years to 65 years.

Patients are stratified into 3 groups based on their functional status and presence or absence of comorbidities: frail patients with significant comorbidity, patients ≥65 years or younger patients with significant comorbidities, and patients <65 years without significant comorbidities.

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

First-line Therapy: Preferred Regimens

Chlorambucil Plus CD20 Monoclonal Antibody

The results of the CLL11 study established chlorambucil plus obinutuzumab as the new standard of care for both elderly patients and for patients with comorbidities lacking del(17p) or *TP53* mutation.[90,91] In this study, 781 patients with comorbid conditions (defined as CIRS score >6 or an estimated CrCl of 30–69 mL/min) were randomized to receive chlorambucil (n = 118), chlorambucil plus obinutuzumab (n = 333), or rituximab plus chlorambucil (n = 330).[90] The combination of chlorambucil plus obinutuzumab and chlorambucil plus rituximab resulted in significant improvement in the median PFS compared to chlorambucil alone (27 months, 16 months, and 11 months, respectively, for chlorambucil plus obinutuzumab, chlorambucil plus rituximab, and chlorambucil alone; $P < .001$).[90] The survival benefit was seen in all of the subgroups except in patients with del(17p). After the median observation time of 39 months, chlorambucil plus obinutuzumab significantly prolonged median PFS (29 months vs. 16 months; $P < .001$), and median time to next treatment (51 months vs. 38 months; $P < .0001$) compared to chlorambucil plus rituximab. There was also a trend towards OS benefit for obinutuzumab.[91] Neutropenia (35%), infusion-related reactions (21%), thrombocytopenia (11%), and infections (11%) were the frequent grade 3 or higher toxicities with chlorambucil plus obinutuzumab. Neutropenia (28%) and infections (14%) were the most frequent grade 3 or higher toxicities associated with chlorambucil plus rituximab.

Based on the results of the CLL11 study, chlorambucil plus obinutuzumab is included as an option with a category 1 recommendation for frail patients with significant comorbidity and patients ≥65 years or younger patients with significant comorbidities.[91]

The safety and efficacy of chlorambucil plus ofatumumab as a first-line treatment for patients with untreated CLL who were not candidates fludarabine-based therapy due to advanced age and/or comorbidities was confirmed in a multicenter phase III study (COMPLEMENT 1; 447 patients were randomized to chlorambucil plus ofatumumab vs.

chlorambucil monotherapy).[92] After a median follow-up of 29 months, the median PFS was significantly longer for ofatumumab plus chlorambucil compared to chlorambucil monotherapy (22 months vs. 13 months; *P* < .001). The median OS was not reached in both arms. Ofatumumab plus chlorambucil also resulted in higher overall response rate (ORR) (82% vs. 69%, *P* = .001) and superior CR rate (12% vs. 1%) compared to chlorambucil alone. Chlorambucil plus ofatumumab is indicated for the treatment of previously untreated CLL in patients for whom fludarabine-based therapy is considered inappropriate.

Chlorambucil plus ofatumumab or rituximab is included with a category 2A recommendation for frail patients with significant comorbidity and patients ≥65 years or younger patients with significant comorbidities. Chlorambucil plus ofatumumab would be an appropriate treatment option for patients who are not candidates for fludarabine-based therapy due to advanced age and/or comorbidities.[92] Chlorambucil plus rituximab should be reserved for patients who cannot tolerate obinutuzumab.[93,94]

Ibrutinib

Ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase (BTK), initially approved for relapsed or refractory CLL, also has demonstrated activity in untreated CLL or SLL.[95-97] The efficacy and safety of ibrutinib in patients ≥65 years with untreated CLL or SLL without del(17p) was demonstrated in a randomized phase III study (RESONATE-2; 269 patients were randomized to receive ibrutinib or chlorambucil as first-line therapy).[95] After a median follow-up of 29 months, ibrutinib resulted in significantly higher ORR (92% vs. 36%; *P* < .0001) and significantly longer PFS (89% vs. 34% at 24 months; *P* < .0001) compared to chlorambucil. With 41% of patients switching to ibrutinib, the estimated 2-year OS rates in the intent-to-treat population were 95% and 84%, respectively, for patients treated with ibrutinib and chlorambucil.[96]

Based on the results of the RESONATE-2 study, ibrutinib is included with a category 1 recommendation for frail patients with significant comorbidity (not able to tolerate purine analogs) and for patients ≥65 years or younger patients with significant comorbidities.[95,96]

Ibrutinib is approved for first-line therapy for all patients, although the efficacy of ibrutinib as first-line therapy in patients <65 years without del(17p) or *TP53* mutation has not been established in randomized clinical trials. The panel acknowledged that there are no data to support the inclusion of ibrutinib with a category 1 recommendation for patients <65 years since the RESONATE-2 study (based on which the FDA approved ibrutinib for first-line therapy in all patients with CLL/SLL) established the efficacy of ibrutinib as first-line therapy only in patients ≥65 years without del(17p).[95,96] However, with the recent FDA approval, some panel members agreed that ibrutinib may be an appropriate option (instead of chemoimmunotherapy) for younger patients with unmutated *IGHV* who do want to enroll in a clinical trial. Therefore, the panel included ibrutinib with a category 2A recommendation for patients <65 years without del(17p) or *TP53* mutation.

See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with ibrutinib.

Fludarabine, Cyclophosphamide, and Rituximab

The fludarabine, cyclophosphamide, and rituximab (FCR) regimen results in high response rates and improved OS in specific subgroups of fit patients with previously untreated CLL/SLL, especially in those with mutated *IGHV*.[31,98,99]

In a large, international, randomized, phase III clinical trial (CLL8 study), 817 physically fit patients with previously untreated CLL (median age 61 years) were randomized to receive up to 6 courses of either the FCR (n = 408) or FC (n = 409) regimen.[31] The FCR regimen resulted in higher ORR (90% vs. 80%; *P* < .001) and CR rate (44% vs. 22%; *P* < .001) compared with FC. After a median follow-up of 6 years, the median PFS was 57 months and 33 months, respectively, for FCR and FC (*P* < .001). The median OS was not reached for FCR and was 86.0 months for FC (*P* = .001). FCR was associated with a statistically significant survival benefit compared to FC in patients <65 years (5-year OS rates were 81% and 69%, respectively; *P* = .002). The corresponding 5-year OS rates were 74% and 62%, respectively, in patients ≥65 years (*P* = .288). The incidence of prolonged neutropenia was significantly higher with the FCR regimen than with FC during the first year after treatment (17% vs. 9%; *P* = .007).

In a phase II study of 300 patients with previously untreated CLL, at a median follow-up of 13 years, the ORR was 95% (72% CR).[98] The overall 13-year PFS rate was 31% (54% for patients with mutated *IGHV* and 9% for patients with unmutated *IGHV*). MRD negativity was achieved in 51% of patients with mutated *IGHV,* with a PFS rate of 80% at 13 years. In a multivariable analysis, unmutated *IGHV* and del(17p) by conventional karyotyping were significantly associated with inferior PFS. Long-term PFS was notable particularly for patients with mutated *IGHV*, with a plateau on the PFS curve beyond 10 years.

The final analysis of the CLL10 study confirmed the superiority of FCR over BR as first-line therapy for CLL without del(17p) in fit patients (n = 567; CIRS score ≤6, CrCl >70 mL/min).[99] The median age was 62 years, but a significantly higher proportion of patients were >65 years in the BR arm (39% vs. 30%). After a median follow-up of 37 months**,** the ORR was 95% for FCR and 96% for BR (*P* = 1.0) with no difference in OS (3-year OS rate was 91% for FCR vs. 92% for BR; *P* = .89). FCR resulted in higher CR rate (40% vs. 31%), more MRD negativity (59% vs. 26% at 12 months; *P* < .0001; 55% vs. 27% at 18 months; *P* = .002), and longer median PFS (55 months vs. 42 months; *P* = .0003) compared to BR. The PFS benefit of FCR was significant in physically fit patients <65 years and in patients with mutated *IGHV*. The median PFS was 54 months and 39 months, respectively, for FCR and BR in patients ≤65 years (*P* = .0004) and there was no significant difference in PFS between the treatment groups for patients >65 years (median not reached for FCR and 48.5 months for BR; *P* = .172). Among patients with a mutated *IGHV,* the median PFS was not reached for FCR compared to 55 months for BR (*P* = .089). The incidence of severe neutropenia and infections were significantly more frequent in the FCR arm (39% vs. 25%), especially in patients older than 65 years.

These results confirm that FCR remains the standard first-line therapy for patients <65 years without significant comorbidities, especially in those with mutated *IGHV*. FCR is included as a preferred treatment option (category 1) for patients <65 years without significant comorbidities. [31,98,99]

An oral formulation of fludarabine was investigated and is approved by the FDA for the treatment of patients with CLL (whose cancer has not responded to or progressed after treatment with at least one alkylating agent).[100-102] However, its use in combination regimens has not yet been established in patients with CLL. Moreover, the efficacy and safety of the oral formulation compared with IV fludarabine has not been established in prospective randomized trials. Therefore, the NCCN Guidelines cannot recommend the appropriate use of oral fludarabine at this time.

Subcutaneous rituximab (rituximab with recombinant human hyaluronidase) in combination with fludarabine and cyclophosphamide (FC) was shown to have similar pharmacokinetic characteristics as IV rituximab in this combination. Rituximab and hyaluronidase human injection for subcutaneous use is approved by the FDA for the treatment of patients with previously untreated and previously treated CLL.[103] Rituximab and hyaluronidase human injection for subcutaneous use may be used in combination with FC regimen after patients have received at least one full dose of intravenous rituximab.

Bendamustine ± CD20 monoclonal antibody

Bendamustine, an alkylating agent, with a low cross-resistance with other alkylating agents was evaluated as first-line monotherapy and in combination with CD20 monoclonal antibody (rituximab, obinutuzumab, or ofatumumab).[104-109]

The safety and efficacy of bendamustine compared to chlorambucil in patients with previously untreated CLL (n = 319) was established in a phase III randomized study. At a median follow-up of 54 months, bendamustine resulted in significantly improved CR rate (21% vs. 11%), median PFS (21 months vs. 9 months; $P < .0001$), and time to next treatment (32 months vs. 10 months; $P < .0001$) compared to chlorambucil.[104] No differences in OS were observed between the two groups. The higher response rates and PFS benefit with bendamustine were retained in the subgroup of patients ≥65 years. The incidences of grade 3 or 4 hematologic toxicities, infections, and gastrointestinal events were higher with bendamustine than with chlorambucil. The efficacy of bendamustine compared to first-line therapies other than chlorambucil has not yet been established.

In another multicenter phase II trial (CLL2M study), the BR regimen induced high response rates (ORR, 88%; CR, 23%) in patients with previously untreated CLL (n = 117; 26% of patients were older than 70 years), with similar response and survival outcomes among the subgroup of elderly patients (age >70 years).[105] After a median observation time of 27 months, the median PFS for all patients was 34 months, and OS rate was 90.5%. Thrombocytopenia (22%), neutropenia (20%), anemia (20%), allergic/infusion reactions (9%), and infections (8%) were the most common grade 3 or 4 toxicities.

In the ongoing phase III randomized trial that is evaluating rituximab and chlorambucil (R-chlorambucil; n = 120) and BR (n = 121) as first-line treatment for CLL in patients who are not candidates for fludarabine-based chemoimmunotherapy (older age or the presence of comorbid conditions), BR was associated with higher ORR (91% vs. 86%) and significantly longer median PFS (40 months vs. 30 months; $P = .003$) than R-chlorambucil.[106] The median OS was not significantly different between the two groups (44 months vs. not calculable). The median follow-up was 24 months. The incidence of adverse events was similar between treatment groups, but the incidence of grade 3 adverse events was higher for BR compared to R-chlorambucil (75% and 64%, respectively). The updated results of the CLL10 study (discussed above) also confirmed that BR is associated with a decreased risk of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).[107] After a median follow-up of 58 months, the incidences of secondary AML and MDS were 3% and 1% in FCR and BR arms, respectively.

Bendamustine in combination with ofatumumab or obinutuzumab has also been evaluated in phase II studies.[108,109] In a phase II study that included 44 patients with untreated CLL (median age 63 years; 13 patients were ≥70 years), bendamustine in combination with ofatumumab resulted in an ORR of 95% (43% CR).[108] With a median follow-up of 29 months, the median PFS was not reached and the

estimated 28-month PFS rate was 72%. The regimen was well tolerated with 89% of patients receiving all 6 cycles and grade 3/4 adverse events were reported in 57% of patients. A phase II study evaluating bendamustine with obinutuzumab in patients with previously untreated CLL (n = 102) also reported an ORR of 89% (49% CR), after a median follow-up of 11 months.[109] Neutropenia was the most common grade 3 or 4 adverse event (27%), and the incidence of grade 3 or 4 infections was reported in 12% of patients.

Bendamustine ± CD20 monoclonal antibody may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is included as an option for patients ≥65 years or younger patients with significant comorbidities and for patients <65 years without significant comorbidities.

First-Line Therapy: Other Recommended Regimens

Fludarabine Plus Rituximab

Fludarabine with concurrent or sequential administration of rituximab was evaluated in the CALGB 9712 study in patients with untreated CLL.[30,110] The concurrent regimen was associated with a higher rate of overall response (ORR; 90% vs. 77% for the sequential regimen) and CR (47% vs. 28%) at the expense of higher incidence of grade 3 or 4 toxicity (primarily comprising neutropenia and infusion-related events).[110] After a median follow-up of 117 months, the median PFS (42 months) and OS (85 months) were similar for the two treatment groups and the estimated 5-year PFS rate was 27%.[30] Comparison of the outcomes of patients treated with fludarabine alone in the CALGB 9011 trial with the pooled results from the CALGB 9712 study suggested that the addition of rituximab to fludarabine prolongs PFS and OS.[111]

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

HDMP Plus Rituximab

In a small cohort of patients with previously untreated CLL (n = 28; median age was 65 years), high-dose methylprednisolone (HDMP) plus rituximab resulted in a 96% ORR with CR in 32% of patients. At a median follow-up of 36 months, the median PFS was 31 months and OS rate was 96%.[112] In the small subgroup of patients aged >70 years (n = 8), the ORR was 100% and 3 patients achieved a CR (38%). HDMP plus 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 hypogammaglobulinemia and infections).

HDMP plus rituximab is included with a category 2B recommendation for all patients, regardless of patient's age and comorbidities.

Pentostatin, Cyclophosphamide, and Rituximab

Pentostatin, cyclophosphamide, and rituximab (PCR) also has demonstrated activity in patients with untreated CLL.[113,114] However, the PCR regimen does appear to provide an advantage over FCR in terms of efficacy or toxicity.[115] In a community-based, multicenter, phase III randomized trial (n = 184) that compared the safety of PCR with the FCR regimen in patients with previously untreated (80% of patients) or minimally pretreated CLL, the ORRs were similar for PCR and FCR (49% vs. 59%), but the CR rate was lower in the PCR group (7% vs. 14%; *P* = .04).[115] The incidence of grade 3 or 4 infectious

events and neutropenia were similar between treatment arms, with increased incidence of leukopenia and thrombocytopenia in the FCR group.[115]

PCR is included as an option with a category 3 recommendation for patients <65 years without significant comorbidities.

Monotherapy with CD20 Monoclonal Antibody or Chlorambucil

The efficacy of obinutuzumab monotherapy in previously untreated CLL at two different doses (1000 mg vs. 2000 mg) in 80 patients with intact organ function and ECOG PS <3 was evaluated in a phase II study.[116] The median age was 67 years. Obinutuzumab at 2000 mg resulted in higher ORR (67% vs. 49%; *P* = .08), CR, or CR with incomplete cytopenia response (20% vs. 5%) than obinutuzumab at 1000 mg.[116] Infusion-related reaction was the most frequent grade 3 or 4 adverse event in both treatment arms. Additional studies are warranted to determine the durability of response and long-term side effects of obinutuzumab monotherapy in patients with untreated CLL.

Obinutuzumab monotherapy is included with a category 2B recommendation for frail patients with significant comorbidity and for patients ≥65 years or younger patients with significant comorbidities.

With multiple randomized studies showing a survival advantage for combination regimens containing chlorambucil or rituximab compared to monotherapy with either of these agents, the majority of the panel members acknowledged that monotherapy with chlorambucil or rituximab is not an effective first-line treatment even for frail patients with comorbid conditions. However, some panel members felt that given the favorable tolerability profile, monotherapy with rituximab or chlorambucil may be an appropriate treatment option for a small fraction of very frail patients or patients ≥65 years with substantial comorbidities or decreased performance status for whom more intensive regimens are not appropriate.[117,118]

Monotherapy with rituximab or chlorambucil is included with a category 3 recommendation.[117,118]

Relapsed or Refractory Therapy: Preferred Regimens

Based on the results from the phase III randomized clinical trials discussed below, ibrutinib, idelalisib plus rituximab, and venetoclax plus rituximab are included as preferred regimens with a category 1 recommendation for patients with relapsed or refractory disease, regardless of patient's age and comorbidities.

Ibrutinib

The safety and efficacy of ibrutinib in relapsed/refractory CLL/SLL was established in a phase III randomized study (RESONATE); 391 patients with previously treated CLL were randomized to monotherapy with ibrutinib (420 mg once daily) or ofatumumab.[119] The updated results of this study also confirmed that ibrutinib significantly improved ORR, PFS, and OS compared to ofatumumab in patients with relapsed/refractory CLL/SLL who had received at least one prior therapy.[120,121] At a median follow-up of 44 months, the median PFS (not reached vs. 8 months for ofatumumab; *P* < .0001) and 3-year PFS rates (59% vs. 3%) were significantly better for ibrutinib.[121] At the time of this analysis, with 68% of patients randomized to ofatumumab crossing over to ibrutinib, the ORR and 3-year OS rates were 91% and 74%, respectively, for ibrutinib. Major hemorrhage, grade ≥3 atrial fibrillation, and grade ≥3 hypertension occurred in 6%, 6%, and 8% of patients, respectively, and the incidence of most of the grade ≥3 adverse events (neutropenia, pneumonia, and atrial fibrillation) decreased with 4-year follow-up.

See *Special Considerations for the Use of Small Molecule* Inhibitors for the management of toxicities associated with ibrutinib.

Idelalisib Plus Rituximab

Idelalisib (the isoform-selective oral inhibitor of PI3K-delta) has demonstrated promising clinical activity in patients with relapsed or refractory CLL/SLL.[122,123] In the multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with either idelalisib (150 mg) or placebo.[122] The majority of the patients (78%) were ≥65 years, 40% had moderate renal dysfunction (CrCl, <60 mL/min), 35% had poor bone marrow function (grade 3 or higher cytopenias), and 85% had a CIRS score >6. At the first planned interim analysis, the study was stopped early owing to the overwhelming efficacy of idelalisib plus rituximab.[122] At 24 weeks, the PFS rate was 93% and 46% in the idelalisib group and placebo group, respectively. Among patients with relapsed CLL with coexisting conditions, idelalisib plus rituximab significantly improved ORR (81% vs. 13%; *P* < .001), PFS (not reached in the idelalisib group vs. 6 months in the placebo group), and OS at 12 months (92% vs. 80%; *P* = .02), compared to rituximab plus placebo. Grade 3 or 4 adverse events (pneumonia, pyrexia, and febrile neutropenia) were reported in 40% of patients in the idelalisib group and 35% in the placebo group. The second interim analysis of this study also confirmed the superior safety and efficacy of idelalisib plus rituximab in terms of ORR, PFS, and OS.[123]

Idelalisib plus rituximab is an appropriate treatment option for relapsed/refractory CLL/SLL in patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or grade ≥ 3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).

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

Venetoclax Plus Rituximab

Venetoclax plus rituximab is also active in patients with relapsed or refractory CLL/SLL resulting in an ORR of 86% to 93% and an estimated 2-year PFS rate of 82% to 85%.[124,125] The results of a phase III randomized study (MURANO; n = 348) demonstrated that venetoclax plus rituximab is associated with superior outcomes compared to BR in patients with relapsed/refractory CLL.[125] After a median follow-up of 24 months, ORR (93% vs. 68%; *P* < .0001), CR rates (27% vs. 8%; *P* < .0001), the median PFS (not reached vs. 17 months; *P* < .0001), and the estimated 24-month PFS rate (85% vs. 36%), were significantly higher for venetoclax plus rituximab than for BR. The incidence of grade 3 or 4 neutropenia (58% vs. 39%) and grade ≥3 TLS (3% vs. 1%) were higher with venetoclax plus rituximab. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of tumor lysis syndrome (TLS) associated with venetoclax.

Relapsed/Refractory Therapy: Other Recommended Regimens

Acalabrutinib

Acalabrutinib, a second-generation BTK inhibitor, demonstrated activity in patients with relapsed or refractory CLL.[14,126] In a phase II study of 134 patients with relapsed/refractory CLL, after a median follow-up of

20 months, the ORR was 85% (ORR including PR with lymphocytosis was 93%), the estimated median PFS was not reached, and the 18-month PFS rate was 88%.[126] Patients with ibrutinib intolerance have also been successfully treated with acalabrutinib without recurrence of symptoms.[127] In a cohort of 33 patients with ibrutinib intolerance, after a median follow-up of 10 months, the ORR (including PR with lymphocytosis) was 76% and the median PFS has not been reached. Headache, diarrhea, upper respiratory tract infection, fatigue, nausea, arthralgia and pyrexia, and weight increase were the most common adverse events of any grade observed in ≥20% of patients. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with acalabrutinib.

Acalabrutinib is included as an option for relapsed/refractory therapy, regardless of patient's age and comorbidities. Acalabrutinib should not be used for ibrutinib-refractory CLL with *BTK C481S* mutations.

Alemtuzumab With or Without Rituximab

Alemtuzumab (subcutaneous or intravenous), either as monotherapy or in combination with rituximab, has demonstrated activity in patients with fludarabine-refractory CLL.[128-132] In a phase II study of 93 patients with fludarabine-refractory CLL, alemtuzumab monotherapy resulted in an ORR of 33% (CR, 2%).[128] The median time to progression was 4.7 months for all patients (9.5 months for patients whose cancer responded to treatment) and the median OS was 16 months (32 months for patients whose cancer responded to treatment).[128] The results of the CLL2H trial showed that subcutaneous alemtuzumab is also effective for the treatment of fludarabine-refractory CLL resulting in an ORR of 34%. At a median follow-up of 38 months, the median PFS, OS, and time to treatment failure (TTTF) were 8 months,19 months, and 6 months, respectively.[129] In a retrospective analysis that included 202 patients with pretreated CLL, alemtuzumab was associated with a favorable ORR (32%), median PFS (6.2 months), and OS (21 months).[131] Myelosuppression and infections were the most common grade 3-4 toxicities. Alemtuzumab plus rituximab results in a higher ORR (53%) than that observed with alemtuzumab monotherapy and there was no significant difference in response rates between patients with fludarabine-sensitive and fludarabine-refractory disease.[132]

Alemtuzumab ± rituximab is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities. However, it should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.[128,131]

Bendamustine and Rituximab With or Without Idelalisib or Ibrutinib

In a phase II trial of GCLLSG, the BR regimen resulted in an ORR of 59% (CR rate, 9%) in patients with relapsed CLL (n = 78; median 2 prior therapies).[133] The ORR among the subgroup (n = 22) with fludarabine-refractory disease was 46%. After a median follow-up of 24 months, the median PFS and OS for all patients were 15 months and 34 months, respectively. The most common grade 3 or 4 adverse events included hematologic toxicities (50% of patients) and infections (13%; all grade 3 events).[133]

The results of recent phase III trials have shown that the addition of idelalisib or ibrutinib to BR significantly improves PFS in patients with relapsed or refractory CLL.[134,135] In the HELIOS trial that evaluated BR plus ibrutinib in 578 patients with previously treated CLL or SLL (≥18 years of age), PFS was significantly improved in patients treated with BR plus ibrutinib compared to those treated with BR plus placebo (not reached vs. 13 months; $P < .0001$).[134] The PFS at 18 months (as assessed by the independent review committee) was 79% and 24%, respectively. In a phase III randomized study of 416 patients with

relapsed or refractory CLL (42% of patients were ≥65 years of age), at a median follow-up 14 months, the median PFS was 21 months for BR plus idelalisib versus 11 months for BR plus placebo ($P < .0001$).[135] The incidence of opportunistic infections and severe adverse events were more frequent in the idelalisib arm.

BR with or without idelalisib or ibrutinib is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities.

Fludarabine, Cyclophosphamide, and Rituximab or Pentostatin, Cyclophosphamide, and Rituximab

The results of the phase III randomized REACH trial confirmed that the addition of rituximab to fludarabine that compared FCR versus FC in patients with CLL at first relapse (n = 552; patients were excluded if they had received prior FC regimen or prior rituximab and patients were required to have fludarabine sensitive disease at relapse), FCR was associated with significantly improved median PFS (based on investigator assessment) compared with the FC arm (31 months vs. 21 months; $P < .001$), although OS was not significantly different between the treatment regimens.[136] The median PFS (27 months vs. 22 months; $P = .022$), ORR (61% vs. 49%; $P < .005$), and CR rate (9% vs. 3%; $P < .005$) as assessed by an independent review committee were also significantly higher with the FCR regimen. The final analysis of a phase II study that evaluated FCR in patients with relapsed or refractory CLL (n = 284; median 2 prior therapies) confirmed the safety and efficacy of this regimen in patients without high-risk features (refractory to prior therapy or chromosome 17 abnormalities).[137] The ORR was 74% with a CR rate of 30% and the median PFS was 21 months. After a median follow-up of 43 months, the estimated median survival was 47 months. The most common adverse events with FCR were hematologic toxicities, including grade 3 or 4 neutropenia associated with 56% of treatment cycles and grade 3 or 4 thrombocytopenia in 20% of cycles. Pneumonia or sepsis was reported in 16% of patients. The subgroup of patients with fludarabine-refractory disease (n = 54) had a significantly lower ORR (56% vs. 79%; $P < .001$) and CR rate (7% vs. 39%; $P < .001$) compared with fludarabine-sensitive patients; the median PFS (8 months vs. 28 months; $P < .001$) and OS (38 months vs. 52 months; $P < .05$) were also significantly decreased among patients with fludarabine-refractory CLL.[137] In addition, the subgroup of patients (n = 20) with chromosome 17 abnormalities (based on standard karyotyping) had worse outcomes with an ORR of 35% (no CR), median PFS of 5 months, and median survival of only 10.5 months. These findings suggest that FCR is a more appropriate treatment option for patients who have received fewer prior therapies (<4 prior regimens) and have fludarabine-sensitive disease, with no chromosome 17 abnormalities.[137]

The PCR regimen is also safe and effective in patients with previously treated CLL. In a small series of patients with relapsed or refractory CLL (n = 32), PCR resulted in an ORR of 75%, among patients with fludarabine-refractory disease.[138]

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

Fludarabine, Cyclophosphamide, and Ofatumumab

In the COMPLEMENT 2 study that evaluated the combination of FC plus ofatumumab (n = 183) versus FC alone (n = 182) in patients with relapsed CLL (median age 61 years; 134 patients (37%) >65 years), FC plus ofatumumab was associated with improved PFS with manageable safety profile. The median PFS (primary endpoint; assessed by the independent review committee) was 29 months and 19

months, respectively, for the combination of FC plus ofatumumab and FC (*P* = .0032).[139] There was no significant difference in OS between the treatment arms. The incidences of grade ≥3 adverse events were 74% and 69%, respectively, for the two treatment groups. Neutropenia was the most common adverse event reported in 49% of patients treated with FC plus ofatumumab and in 36% of patients treated with FC. Based on the results of this study, the FDA approved the combination of FC plus ofatumumab for the treatment of patients with relapsed CLL.

FC plus ofatumumab is included as an option for relapsed/refractory therapy, for patients <65 years without significant comorbidities.

HDMP Plus rituximab

In small studies, HDMP combined with rituximab was effective in patients with heavily pretreated CLL (including fludarabine-refractory disease), resulting in an ORR of 93% (CR in 14%–36% of patients) and a median PFS of 7 to 15 months.[140,141] The regimen was associated with infectious complications (including opportunistic fungal infections) in about 30% of patients, which may necessitate adequate antiinfective prophylaxis and close monitoring for early signs of infections.[140,141]

HDMP plus rituximab is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities.

Idelalisib

In a phase I study of 54 patients with relapsed/refractory CLL, idelalisib monotherapy resulted in an ORR of 72% (39% PR and 33% PR with treatment-induced lymphocytosis). The median PFS was 16 months and the median OS was not reached with 75% of patients surviving at 36 months.[13] A post hoc analysis of 39 patients with relapsed or refractory SLL enrolled in phase I (n = 11) and phase II (n = 28) studies (that evaluated the efficacy and safety of idelalisib patients with relapsed- or refractory-indolent NHL) showed that idelalisib monotherapy has substantial clinical activity in the subset of patients with relapsed or refractory SLL.[142] The ORR was 55% (6 out of 11) and 61% (17 out of 28), respectively. The median duration of response was 2.3 months and 12.5 months, respectively. The median PFS was 4 months and 11 months, respectively.

Idelalisib monotherapy is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with idelalisib.

Lenalidomide With or Without Rituximab

Lenalidomide monotherapy or in combination with rituximab has also shown activity in relapsed/refractory CLL.[143-145] In a phase II study of 59 patients with relapsed or refractory CLL, lenalidomide in combination with rituximab resulted in an ORR of 66% with CR in 12%.[143] The median OS was not reached, with an estimated 3-year OS rate of 71%. However, the ORR was lower for the subgroup of patients with fludarabine-refractory CLL compared with those with fludarabine-sensitive CLL (33% vs. 70%; *P* = .04). The most common grade 3 or 4 toxicity included neutropenia (74%), thrombocytopenia (34%), and infections or febrile episodes (24%). Tumor flare reactions (grade 1 or 2) occurred in 27% of patients. In the prospective, multicenter, randomized phase II trial of 103 patients with relapsed/refractory CLL (CLL-009 trial), at a median follow-up of 24 months, lenalidomide monotherapy resulted in an ORR of 40%. The median PFS and OS were 10 months and 33 months, respectively.[144] The median PFS and OS were significantly different between patients with CLL responding to lenalidomide and patients with stable disease (median PFS: 27 vs. 7 months, *P* < .001; median OS: not reached vs.

19.8 months; *P* = .011). Myelosuppression and tumor flare reactions were the most common grade 3 or 4 adverse events.

Lenalidomide with or without rituximab is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities. 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. A randomized phase III study (ORGIN trial) evaluating monotherapy with lenalidomide vs. chlorambucil as initial therapy for CLL in patients >65 years was halted by the FDA due to concerns for increased risk of death in the lenalidomide arm versus chlorambucil arm.[146] Lenalidomide is not recommended as initial therapy.

Obinutuzumab or Ofatumumab Monotherapy

The results of the GAUGIN study confirmed that obinutuzumab has monotherapy activity in patients with heavily pretreated relapsed or refractory CLL.[147] In this study of 20 patients, obinutuzumab at a fixed dose of 1000 mg resulted in a best ORR of 30%; median PFS and duration of response were 10.7 months and 8.9 months, respectively.

Ofatumumab has demonstrated activity in patients with fludarabine-refractory CLL with bulky lymphadenopathy.[148,149] In the final analysis from the pivotal international clinical trial (n = 207; 95 patients with fludarabine- and alemtuzumab-refractory CLL [FA-ref CLL] and 112 patients with fludarabine-refractory CLL with bulky lymphadenopathy [>5 cm; BF-ref CLL]), ofatumumab monotherapy resulted in an ORR of 49% in patients with FA-ref CLL and 43% in those with BF-ref CLL.[149] The median PFS was 5 months and 6 months, respectively, for patients with FA-ref CLL and BF-ref CLL. The median OS was 14 months and 17 months for the FA-ref and the BF-ref groups, respectively. The most common ≥ grade 3 adverse events were infections (24%) and neutropenia (12%). An ad hoc retrospective analysis of patients with FA-ref CLL (n = 96) and BF-ref CLL (n = 112) showed that ofatumumab was also effective and well tolerated in patients with FA-ref CLL and previous rituximab exposure.[150] The ORR was 43%, 44%, and 53%, respectively, for CLL with previous rituximab exposure, rituximab-refractory CLL, and rituximab-naive CLL. The median PFS was 5.3, 5.5, and 5.6 months, respectively, and median OS was 15.5, 15.5, and 20 months, respectively.

Obinutuzumab or ofatumumab monotherapy is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities.

Venetoclax

Venetoclax monotherapy has also shown promising activity in patients with relapsed or refractory CLL after prior treatment with ibrutinib or idelalisib, resulting in an ORR of 65% and 67%, respectively.[151,152] The median PFS has not yet been reached, and the estimated 12-month PFS rate was 79% for patients with relapsed or refractory CLL after prior treatment with idelalisib.[152] The most common grade 3 or 4 adverse events were neutropenia, thrombocytopenia, anemia, and decreased lymphocyte count.

Venetoclax monotherapy is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of TLS associated with venetoclax.

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

First-line Therapy: Preferred Regimens

Ibrutinib

Enrollment in an appropriate clinical trial is recommended for patients with del(17p) CLL. In the absence of a clinical trial, ibrutinib is the

preferred treatment option. In a phase II trial that included 35 treatment-naïve patients with del(17p)/*TP53* mutation (median age 62 years), at a median follow-up of 24 months, ibrutinib resulted in objective responses in 32 of 33 evaluable patients (55% of patients had a PR and 42% of patients had a PR with lymphocytosis) and the estimated OS at 24 months was 84%.[153] The cumulative incidence of progression at 24 months was 9%. Grade ≥3 neutropenia, anemia, and thrombocytopenia were reported in 24%, 14%, and 10% of patients, respectively. Grade 3 pneumonia and rash were reported in 6% and 2% of patients, respectively. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with ibrutinib.

Continuation of treatment with ibrutinib (until disease progression) is recommended for patients with responding disease. At time of disease progression on ibrutinib, transition to alternate therapy should be done as soon as possible upon stopping ibrutinib since progression may accelerate when ibrutinib is stopped. Treatment-free interval should be as short as possible.

First-line Therapy: Other Recommended Regimens

The panel emphasizes that the efficacy of ibrutinib in del(17p) CLL exceeds that of the other recommended regimens and should be considered as the best choice in the absence of a contraindication to give this treatment. Based on the data from clinical studies (discussed below), alemtuzumab with or without rituximab, HDMP plus rituximab, and obinutuzumab monotherapy are included as options when ibrutinib is not deemed to be appropriate.

Alemtuzumab With or Without Rituximab

Alemtuzumab, initially approved for fludarabine-refractory CLL, has also shown activity as a first-line treatment for patients with CLL.[154-157] In an international, multicenter, randomized phase III study (CAM307), 297 patients with previously untreated CLL were randomized to receive alemtuzumab or chlorambucil.[155] Alemtuzumab resulted in a significantly higher ORR (83% vs. 55%; $P < .0001$) and CR rate (24% vs. 2%; $P < .0001$) than chlorambucil and a modest but statistically significant survival benefit compared with chlorambucil (median PFS was 15 months vs. 12 months; $P = .0001$). Alemtuzumab was also associated with higher ORR (64% vs. 20%) and longer median PFS (11 months vs. 2 months) in the small subgroup of 21 patients with del(17p). After a median follow-up of 25 months, median OS was not reached for either treatment arm; no significant difference in survival was reported between treatment arms.[155] Infusion-related events, CMV infections, and grade 3 or 4 neutropenia (41% vs. 25%) were higher with alemtuzumab compared with chlorambucil.

HDMP Plus Rituximab

HDMP in combination with rituximab has demonstrated activity in a small cohort of 28 patients with previously untreated CLL with poor-risk factors at baseline (eg, high-risk Rai stage in 48%; unmutated *IGHV* in 57%; cytogenetic abnormalities in 39%, including del11q and del17p).[112]

Obinutuzumab Monotherapy

In the phase II study that demonstrated significant efficacy of obinutuzumab monotherapy in patients with untreated CLL (n = 80), del(17p) and del(11q) were present in 10% and 12% of patients, respectively.[116] Obinutuzumab monotherapy (at dose levels of 2000 mg and 1000 mg) resulted in an ORR rate of 67% and 49%, respectively.

Relapsed/Refractory Therapy: Preferred Regimens

Ibrutinib

The results of the RESONATE-17 phase II study confirmed the safety and efficacy of ibrutinib in 145 patients with relapsed or refractory del(17p) CLL.[158] At a median follow-up of 12 months, the ORR (as assessed by the independent review committee) was 83%. In an extended analysis with a median follow-up of 28 months, the investigator-assessed ORR and the 24-month PFS and OS rates were 83%, 63%, and 75%, respectively.[158] The subgroup analysis of the RESONATE study also showed that the presence of del(17p) or *TP53* mutation was not associated with inferior PFS outcomes.[120] The ORR and 18-month PFS rates were 89% and 71%, respectively, for patients with del(17p) compared to 91% and 79% for those without del(17p). The ORR and 18-month PFS rates were 91% and 66% for patients with *TP53* mutation compared to 92% and 81% for those without *TP53* mutation. The estimated 18-month OS rate was 83% for the del(17p) subgroup and 79% for those with complex karyotype.

Based on these results, the panel has included ibrutinib with a category 1 recommendation. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with ibrutinib.

Venetoclax With or Without Rituximab

In a phase II study of 107 patients (61 patients ≥65 years; 46 patients <65 years) with relapsed or refractory del(17p) CLL, at a median follow-up of 12.1 months, venetoclax resulted in an ORR of 79.4% as assessed by the independent review committee.[159] The ORR was also high (>70%) in all subgroups of patients with additional risk features (eg, fludarabine-refractory status, bulky disease, del(17p), *TP53* mutation). The estimated 12-month PFS and OS rates were 72% and 86.7%, respectively. Neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%) were the most common treatment-related adverse events. Venetoclax is approved for the treatment of relapsed or refractory del(17p) CLL.

In the phase III randomized MURANO study that compared venetoclax plus rituximab and BR in patients with relapsed/refractory CLL, venetoclax plus rituximab was superior to BR in prolonging PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation.[125] Del(17p) and *TP53* mutation were present in 27% and 25% of patients, respectively, in patients randomized to venetoclax plus rituximab and in 27% and 28% of patients, respectively, in patients randomized to BR.

Based on these results, venetoclax plus rituximab is included with a category 1 recommendation and venetoclax monotherapy is included with a category 2A recommendation. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of TLS associated with venetoclax.

Idelalisib Plus Rituximab

The second interim analysis of the phase III randomized study that evaluated idelalisib plus rituximab confirmed that this regimen also retained efficacy in patients with high-risk features such as del(17p) or *TP53* mutations (43% of patients had del(17p)/TP53 mutation); unmutated *IGHV*, ZAP70, and CD38 expression; and beta-2 microglobulin (>4 mg/L).[123] At 12 months, the estimated PFS rate was 62% and the median OS was not reached for patients with del(17p) or *TP53* mutation or del(11q) compared to 74% and not reached for patients without any of these cytogenetic abnormalities.

Idelalisib plus rituximab is included as an option with a category 2A recommendation. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with idelalisib.

Relapsed/Refractory Therapy: Other Recommended Regimens

The regimens discussed below are included as options for relapsed/refractory therapy based on the results from retrospective analyses or subgroup analyses from the prospective clinical trials that had included patients with del(17p) or *TP53* mutation. However, it should be noted that these were not sufficiently powered to evaluate the efficacy and safety of regimens in patients with del(17p) or *TP53* mutation.

Acalabrutinib

In the phase II study that evaluated acalabrutinib in relapsed/refractory CLL, acalabrutinib was associated with an ORR of 85% in patients with relapsed/refractory del(17p) CLL.[126] The median PFS was not reached and the 18-month PFS rate was 78%.

Alemtuzumab With or Without Rituximab

In the CLL2H trial that evaluated subcutaneous alemtuzumab for the treatment of fludarabine-refractory CLL, none of the poor-prognosis genetic abnormalities including del(17p) or *TP53* mutation were associated with significant differences in response rates or survival.[129] Among patients with del(17p) CLL, the median OS and TTF were 18 months and 6 months, respectively. As discussed earlier, the addition of rituximab results in higher response rates than alemtuzumab monotherapy in patients with fludarabine-refractory CLL.[132]

HDMP Plus Rituximab

HDMP in combination with rituximab is also effective for relapsed CLL with unfavorable cytogenetic features (n = 27; 9 patients had del(17p)) resulting in objective responses of 78% of patients (including 5 out of 9 patients with del(17p)), and the 3-year survival rate was 41%.[160] Infectious complications developed in 29% of patients, which may necessitate adequate antiinfective prophylaxis and close monitoring for early signs of infections.

Idelalisib

In a phase I study that evaluated idelalisib monotherapy in 54 patients with relapsed/refractory CLL with adverse characteristics, idelalisib monotherapy resulted in an ORR of 54% (7 out of 13 patients) in patients with del(17p) and/or *TP53* mutation and the median PFS was 3 months.[13]

Lenalidomide With or Without Rituximab

In the CLL-009 trial, lenalidomide monotherapy also showed modest activity resulting in an ORR of 22% and 36%, respectively, in patients with relapsed/refractory CLL with del(17p) and *TP53* mutation.[144] Although the ORR was lower for patients with del(17p) (22% vs. 47% for those without del(17p); *P* = .049), there were no significant differences in PFS (5 months vs. 11 months; *P* = .171) and OS (19 months vs. 35 months; *P* = .318) between these two groups.

Lenalidomide with rituximab also has modest activity resulting in an ORR of 53% in patients with relapsed/refractory del(17p) CLL, which was not significantly different from the ORR in patients without del(17p) (70%; *P* = .35). The TTF was also not significantly different between the groups of patients with del(17p) and other cytogenetic risk features, although this subgroup analysis is limited by small subgroup size.[143]

Ofatumumab

In the international, multicenter study that evaluated ofatumumab monotherapy in patients with FA-ref CLL and BF-ref CLL, ofatumumab resulted in an ORR of 41% among patients with FA-ref CLL with del(17p).[148] However, the ORR was only 14% among patients with BF-ref CLL with del(17p). Among all characteristics evaluated, del(17p) was the only factor associated with lower response rate in patients with BF-ref CLL.

Ofatumumab is included as an option for relapsed/refractory CLL with del(17p). However, it is not effective for patients with lymph nodes >5 cm.

First-line Consolidation Therapy

The CLLM1 study demonstrated the feasibility and efficacy of lenalidomide maintenance after first-line therapy.[161] In this study, 89 patients with a poor outcome after first-line chemoimmunotherapy (those who achieved at least a PR to first-line therapy with MRD levels of $\geq 10^{-2}$ or MRD levels of $\geq 10^{-4}$ to $<10^{-2}$ with either an unmutated *IGHV*, del(17p) or *TP53* mutation at baseline) were randomized to receive either lenalidomide maintenance (n = 60) or placebo (n = 29). After a median observation time of 18 months, the median PFS was 13 months in the placebo arm and was not reached in the lenalidomide arm. The incidences of treatment-related adverse events such as hematologic toxicity (50% vs. 17%), gastrointestinal disorders (61% vs. 28%), and skin disorders (63% vs. 28%) were more frequent with lenalidomide.

Lenalidomide maintenance after first-line therapy is included as an option under *Other Recommended Regimens* for high-risk patients (MRD ≥10-2 or ≥10-4 and <10-2 with unmutated *IGHV*).

Second-line Consolidation Therapy

The phase III randomized trial (PROLONG) evaluated the efficacy and safety of ofatumumab maintenance versus observation for patients in remission after second-line therapy for CLL.[162] In this study, 474 patients with relapsed CLL in CR or PR after second-line or third-line therapy were randomized to receive ofatumumab maintenance or observation. At a median follow-up of 19.1 months, ofatumumab maintenance resulted in improved PFS compared to observation (29.4 months vs. 15.2 months; $P < .0001$). Neutropenia (24%) and infections (13%) were the most common grade ≥3 adverse events associated with ofatumumab maintenance. Ofatumumab maintenance is approved for patients with recurrent or progressive CLL who are in CR or PR after two or more lines of prior therapy.

The phase III randomized multicenter trial (CONTINUUM trial) demonstrated the feasibility and efficacy of lenalidomide maintenance after second-line therapy.[163] In this trial, 314 patients with at least a PR to second-line therapy were randomized to receive either lenalidomide maintenance or placebo. After a median follow-up of 31.5 months, the median PFS was significantly longer for lenalidomide compared to placebo (34 months vs. 9 months). There was no significant difference in OS between the two groups. Neutropenia (60% vs. 23%), thrombocytopenia (17% vs. 6%), and diarrhea (8% vs. <1%) were the most common grade 3 or 4 adverse events in the lenalidomide and placebo arms, respectively.

Lenalidomide maintenance or ofatumumab maintenance is included as an option under *Other Recommended Regimens* with a category 2B recommendation for patients who are in CR or PR to second-line therapy.[162,164]

Allogeneic Hematopoietic Cell Transplant

Long-term results from several prospective studies have shown that allogeneic hematopoietic cell transplant (HCT) can provide long-term disease control and also overcome the poor prognosis associated with del(17p) and *TP53* mutations.[165-172] The results of the prospective multicenter trial (GCLLSG CLL3X study) also showed that nonmyeloablative allogeneic HCT can provide long-term disease control in a significant proportion of patients with poor-risk CLL independent of the presence of *TP53*, *SF3B1*, and *NOTCH1* mutations.[170] The 6-year EFS, OS, and non-relapse mortality rates for patients who underwent allogeneic HCT in this study (n = 90) were 38%, 58%, and 23%, respectively; 54% of patients were relapse-free and MRD-negative at 12 months post-HCT.[170] In a more recent retrospective analysis of 52 patients (21 patients were untreated and 31 had received prior therapy with chemotherapy or immunotherapy) with CLL and del(17p), at 2 years after referral, the OS rate was higher for patients who underwent allogeneic HCT compared to those who did not (64% and 25%, respectively).[172]

It is understood that studies involving allogeneic HCT are subject to significant selection biases. Nonetheless, based on the available evidence, prior to the development of small molecule inhibitors, allogeneic HCT was considered as an effective treatment option for patients with high-risk CLL (disease that is refractory to purine analog-based chemoimmunotherapy or disease relapse within 2 years after treatment with purine analog-based chemoimmunotherapy and/or disease with del(17p) or TP53 mutation).[173] At the present time, given the favorable outcome of patients with del(17p) or TP53 mutation treated with ibrutinib as first-line therapy and the availability of venetoclax as an effective treatment option for relapsed or refractory CLL with del(17p) or TP53 mutation, allogeneic HCT is not considered as a reasonable treatment option for refractory CLL or disease relapse within 12 to 24 months after initial purine analogue–based therapy.[174]

Indications for Allogeneic HCT

Allogeneic HCT can be considered for CLL/SLL refractory to small molecule inhibitor therapy in patients without significant comorbidities.

For patients with CLL/SLL with del(17p) or *TP53* mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if complex karyotype (≥3 abnormalities) is present. However, available data suggest that complex karyotype (≥5 abnormalities) is associated with inferior OS and EFS following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics.[175]

Special Considerations for the Use of Small Molecule Inhibitors

Ibrutinib, acalabrutinib, and idelalisib cause early mobilization of lymphocytes into the blood resulting in a transient increase in absolute lymphocyte count in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks after initiating therapy and may persist for several weeks on treatment.[12] While lymphocytosis can sometimes be profound, clinical consequence (ie, leukostasis) is extremely rare and therapy should be continued. Slow or incomplete resolution of lymphocytosis does not appear to impact outcome as measured by PFS.[12]

Atrial fibrillation (grade ≥3) and major hemorrhage (defined as serious or grade 3 or higher bleeding events or central nervous system hemorrhage of any grade) have been reported in 6% and 4% of patients treated with ibrutinib, respectively.[95] Hypertension (grade ≥3) associated with ibrutinib (reported in 20% of patients) has uncommonly been the

basis for discontinuation and should be managed with anti-hypertensives as appropriate.[176]

Acalabrutinib was not associated with any grade ≥3 bleeding events; grade ≥3 hypertension and atrial fibrillation were observed in 3% and 2% of patients treated with acalabrutinib, respectively.[14,126] Headaches commonly observed with acalabrutinib early in treatment course typically resolve after 1 to 2 months of treatment and generally can be managed with analgesics (eg, acetaminophen) and caffeine supplements.

Monitoring for atrial fibrillation and hypertension along with appropriate management is recommended for patients receiving ibrutinib or acalabrutinib. Switching to alternate therapy should be considered, especially in patients with atrial fibrillation/hypertension that is not medically controllable. The benefit and risk of ibrutinib or acalabrutinib should be evaluated in patients requiring anti-platelet or anticoagulant therapies. Patients requiring warfarin have been excluded from clinical trials evaluating ibrutinib and acalabrutinib. Patients should be monitored for signs of bleeding. Concomitant administration of ibrutinib or acalabrutinib with warfarin should be avoided.

Fatal and/or serious hepatotoxicity (transaminase elevations), severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.[177] Hepatotoxicity is a major concern in younger patients treated with idelalisib as first-line therapy.[178] Close monitoring of transaminase levels is essential and concurrent administration of idelalisib with other hepatotoxic drugs should be avoided. Idelalisib is also associated with increased risk of opportunistic infections (PJP and CMV reactivation) and febrile neutropenia. The addition of CD20 monoclonal antibody or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia.[135] Herpes virus prophylaxis with acyclovir or equivalent, PJP prophylaxis with sulfamethoxazole trimethoprim or equivalent, and routine monitoring for early signs of infectious complications and CMV reactivation (as described below under *Supportive Care*) is recommended for patients receiving idelalisib.

TLS was an important side effect of venetoclax therapy in early clinical trials. Initiation at lower dose (20 mg for one week) and gradual step-wise ramp-up over 5 weeks to target dose (400 mg daily) along with prophylaxis for TLS is recommended to mitigate the risk and frequency of TLS in patients receiving venetoclax.[179] Initiation and accelerated escalation of venetoclax (20 mg to 400 mg over 3 weeks) with close inpatient monitoring for TLS can be done in the subgroup of patients with high tumor burden and where there is concern for rapid disease progression on or following BTK-inhibitor therapy.[151,180] Venetoclax is administered as follows for accelerated escalation: inpatient with close monitoring for TLS, 20 mg on Week (W)1/Day(D)1, 50 mg on W1/D2-3, 100 mg on W1/D4-7 (all inpatient), then outpatient unless concern for TLS, 200 mg on W2/D1-7, and 400 mg on W3/D1-continuous. Additionally, continued BTK inhibition concurrent with initiation and escalation of venetoclax with discontinuation of BTK inhibitor after venetoclax dose escalation to 400 mg daily can be considered.[151,180] 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.

Histologic Transformation and Progression

About 2% to 10% of patients with CLL/SLL will develop histologic transformation (also known as Richter's transformation) to diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma (HL) during the course

of their disease and treatment.[181-183] The incidence of Richter's transformation increases with the number of prior regimens. Inactivation of *NOTCH1*, c-*MYC* abnormalities and disruption of *TP53* and *CDKN2A/B* have been identified as possible genetic pathways involved in the pathogenesis of Richter's transformation.[184-186]

Richter's transformation to DLBCL can either be clonally unrelated to CLL (78%) or clonally related to CLL (22%).[184,187] The clonal relationship can be assessed using *IGHV* gene sequencing and the majority of patients with Richter's transformation to clonally related DLBCL carry unmutated *IGHV.*[187] Richter's transformation to clonally unrelated DLBCL is characterized by a significantly lower prevalence of *TP53* disruption and a significantly longer median survival than clonally related DLBCL (62 months vs. 14 months).[184] Richter's transformation to HL is clinically less aggressive but it is associated with a poor prognosis.[182,183,188] CLL with increased prolymphocytes (CLL-PLL) or CLL with expanded proliferation centers and high Ki-67 proliferative rate (accelerated CLL) are not considered as Richter's transformation, but rather as progression of CLL, associated with a more aggressive disease course.[189]

Diagnosis and Workup

Excisional biopsy is required (if lymph node is accessible) for the diagnosis of Richter's transformation. Core needle biopsy is acceptable, when excisional or incisional lymph node biopsy is not feasible. EBV infection of CLL can produce Reed-Sternberg (RS)-like proliferations. Therefore, biopsy tissue should be evaluated for EBV infection and the presence of morphologic RS cells in a CLL background should not be considered as Richter's transformation. RS-like cells in a background of CLL may progress to classical HL in some patients.[190]

The workup of patients with Richter's transformation or progression is similar to that of patients with CLL/SLL. PET/CT scans are recommended to direct nodal biopsy and biopsies should be directed to lesions with highest FDG uptake on PET scans.[191,192]

Treatment Options

Richter's transformation to clonally unrelated DLBCL (de novo DLBCL) should be managed similarly to DLBCL as outlined in the NCCN Guidelines for B-cell Lymphomas.

Richter's transformation to DLBCL (clonally related or unknown clonal status) is generally managed with chemoimmunotherapy regimens recommended for DLBCL.[188,193] R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) plus rituximab alternating with methotrexate and cytarabine, and oxaliplatin, fludarabine, cytarabine and rituximab (OFAR) are included as treatment options. However, these regimens typically result in poor responses.

In a phase I-II trial that included 20 patients with Richter's transformation, OFAR resulted in an ORR of 50%.[194] The median response duration was 10 months. In the subsequent phase I-II study that included 35 patients with Richter's transformation, a modified OFAR regimen with reduced-dose cytarabine also resulted in an ORR of 39% (7% CR), with a median survival of 7 months.[195] Cytopenias were the most common hematologic toxicities. The modified R-hyperCVAD regimen (rituximab, cyclophosphamide, vincristine, liposomal daunorubicin, dexamethasone) alternating with methotrexate and cytarabine plus rituximab with growth factor support was also active in patients with Richter's transformation (n = 30), resulting in an ORR of

43% (27% CR) and a 12-month survival rate of 28%.[196] However, it was associated with significant toxicity and was not more effective than the modified hyperCVAD regimen alone.[197] In a phase II trial that included 15 patients with Richter's transformation, RCHOP resulted in an ORR of 67% (7% CR).[198] After a median follow-up of 69 months, the median PFS and OS were 10 months and 21 months, respectively. In a retrospective cohort study of 46 patients with Richter's transformation treated with first-line R-EPOCH regimen, the median PFS and OS were 4 months and 6 months, respectively.[199] Complex karyotype was associated with significantly shorter PFS and OS, whereas survival of patients without a complex C karyotype was similar to that of patients with de novo DLBCL.

In a phase II study of 25 patients (16 patients with relapsed CLL and 9 patients with Richter's transformation to DLBCL), pembrolizumab (an immune check point inhibitor) resulted in objective response in 44% of patients with Richter's transformation with disease progression after prior therapy with ibrutinib; the median OS for this cohort of patients was 11 months.[200] At the present time, the panel feels that these data are not sufficient to support the inclusion of pembrolizumab as a treatment option.

Allogeneic HCT can also be considered following a response to initial therapy in patients with Richter's transformation.[174,193,201,202] In a non-randomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic HCT after achieving a CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo allogeneic HCT, or who underwent allogeneic HCT for relapsed or refractory Richter's transformation (75% vs. 27% and 21%, respectively; $P = .019$).[193] In a retrospective analysis that evaluated the outcome after autologous or allogeneic HCT in 59 patients with Richter's transformation, the 3-year estimated OS, 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.[201] In a multivariate analysis, chemotherapy-sensitive disease and reduced-intensity conditioning were found to be associated with superior RFS after allogeneic HCT. Autologous HCT may also be an appropriate therapy for patients with Richter's transformation who have a response to initial therapy but are not a candidate for allogeneic HCT due to age, comorbidities, or lack of a suitable donor.[201]

Richter's transformation to HL should be managed as outlined in the NCCN Guidelines for Hodgkin Lymphoma. Achievement of CR to the ABVD regimen was the most important factor predicting survival of patients with Richter's transformation to HL.[203,204]

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

Supportive Care

Infections

Infectious complications are influenced by the progressive reduction in immunoglobulin levels (hypogammaglobulinemia) and are more common in patients with previously treated CLL.[205,206] Patients with heavily pretreated fludarabine-refractory CLL have high susceptibility to developing serious infections.[207]

IVIG is associated with a significant decrease in the occurrence of infections but with no improvement in OS outcome.[208-212] 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.

Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients.[213] All live vaccines should be avoided. Patients with CLL tend to have poor response to influenza vaccine and should be counseled to exercise care during influenza season even with vaccination. Protein and conjugate vaccines were shown to induce better responses than plain polysaccharide vaccines.[214,215]

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents.[216,217] HBV carriers have high risk of HBV reactivation. Fulminant hepatitis, hepatic failure, and death associated with HBV reactivation have occurred in patients receiving CD20 monoclonal antibody (rituximab, obinutuzumab, or ofatumumab)-containing regimens, including rituximab, obinutuzumab, or ofatumumab.[218] HBV reactivation has also been reported in patients treated with alemtuzumab, ibrutinib, and idelalisib. HBV prophylaxis and monitoring is recommended in high-risk patients receiving CD20 monoclonal antibody, alemtuzumab, purine analogs, ibrutinib, and idelalisib.

HBsAg and HBcAb testing is recommended for all patients receiving CD20 monoclonal antibody therapy. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. Patients receiving IVIG may be HBcAb positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.[219]

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.[220,221] Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes positive, consultation with a hepatologist and discontinuation of CD20 monoclonal antibody therapy is recommended. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of treatment.[222]

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.[223] Current practices for the management of CMV reactivation include the use of prophylactic ganciclovir if CMV viremia is present or the use of ganciclovir if the viral

load is found to be increasing during therapy.[224,225] 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.[226,227] Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias.

Although direct antiglobulin test (DAT) was used for the diagnosis of AIHA, most patients with AIHA have negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA.[228] 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.[228-231] Purine analog-based therapy was associated with AIHA. Recent studies reported higher incidence of AIHA in patients treated with fludarabine or chlorambucil compared to those who received fludarabine-based combination regimens.[228,232] 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.[233] 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.[233]

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine,[234] and splenectomy should be used in steroid-refractory cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias.[235-241] Romiplostim and eltrombopag have shown promising results in the treatment of thrombocytopenia associated with ITP.[242-245] Romiplostim and eltrombopag are FDA-approved for the treatment of thrombocytopenia in patients with ITP that is refractory to steroids, IVIG, and splenectomy.

PRCA is less common in patients with CLL. PRCA can be managed with corticosteroids, cyclophosphamide, cyclosporine, or anti-thymocyte globulin.[227] Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. In the very refractory cases, allogeneic HCT may be necessary. Evaluation of parvovirus B19 is also recommended for all patients with PRCA since patients with evidence of parvovirus B19 infection usually respond well to IVIG.[227]

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. Tumor flare reactions have been reported in approximately 80% of patients with untreated CLL (although these reactions were limited to grade 1 or 2 events) and in approximately 30% to 60% of patients with relapsed or refractory CLL.[246-248] Tumor flare was more frequent among patients with enlarged (>5 cm) lymph nodes at baseline.[246] In patients with relapsed or refractory CLL, the “standard” 25-mg dose of lenalidomide used in patients with multiple myeloma resulted in excessive toxicity (tumor flare, tumor lysis, and myelosuppression) when given as the initial dose.[249] Results from a recent prospective study suggest that initiation of lenalidomide at lower starting doses (5, 10, or 15 mg/d) and subsequent dose escalation by 5 mg up to a maximum of 25 mg/d was associated with an acceptable tolerability profile in patients with relapsed or refractory CLL (n = 103).[144,250]

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 while treated with lenalidomide-containing regimens. 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 a CD20 monoclonal antibody is initiated at least 1 week prior to start of lenalidomide for those patients treated with the combination regimen.

Venous Thromboembolism

Lenalidomide may also be associated with venous thromboembolism (VTE) in patients with CLL/SLL.[246,251] 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

Bulky lymph nodes, progressive disease after small-molecule inhibitor therapy, and patients receiving treatment with venetoclax, chemoimmunotherapy, lenalidomide, and obinutuzumab are considered to be high risk for TLS. TLS prophylaxis as noted in the *Supportive Care* section of the algorithm should be considered for these patients.

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, patient's age, performance status, comorbid conditions, as well as the agent's toxicity profile. Chemoimmunotherapy is a standard first-line therapy for CLL/SLL without del(17p) or *TP53* mutation in specific subsets of patients depending on their age and the presence of comorbidities and offers a defined treatment course with treatment-free interval. Furthermore, the majority of patients with mutated *IGHV* who receive first-line FCR are expected to have more than 10 years of PFS, and may potentially be cured of their disease. Alternatively, ibrutinib is the preferred first-line treatment option for CLL/SLL with del(17p) or *TP53* mutation. Ibrutinib is also a standard option that offers excellent long-term disease control, including in high-risk subgroups such as those with del(11q) and unmutated *IGHV*. Idelalisib is not indicated in first-line treatment. Ibrutinib, idelalisib (with or without rituximab), acalabrutinib, and venetoclax ± rituximab are effective treatment options for relapsed/refractory CLL/SLL with del(17p) or *TP53* mutation. Careful monitoring of adverse events after initiation of treatment and supportive care for the treatment-related complications should be an integral part of CLL/SLL management.

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