National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Version 3.2018 — February 12, 2018

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NCCN Guidelines Version 3.2018 Panel Members
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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NCCN Guidelines Panel Disclosures

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

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

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 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.

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.

Continued

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NCCN Guidelines Version 3.2018 Updates
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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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."

CSLL-4

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

Continued

Updates in Version 3.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

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."

Continued

Updates in Version 3.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

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."

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.

Continued

Updates in Version 3.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

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 $\geq 10^{-2}$ or $\geq 10^{-4}$ 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."

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/m² in cycle 1 with escalation to 90 mg/m² if tolerated), rituximab ± ibrutinib (category 2B). This recommendation was changed from a category 3 to a category 2B recommendation.
      - – Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² 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 $\geq 10^{-2}$ or $\geq 10^{-4}$ 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.

Continued

Updates in Version 3.2018 of the NCCN Guidelines for CLL/SLL from Version 2.2017 include:

Special Considerations for the Use of Small-Molecule Inhibitors

CSLL-F 1 of 2

- 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."

CSLL-F 2 of 2

- 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*."

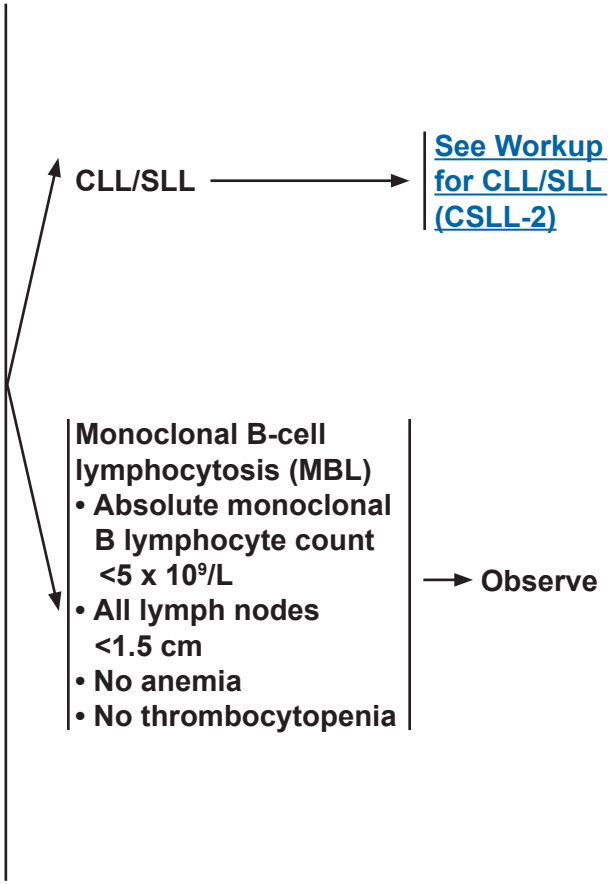
DIAGNOSIS[a]

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]**

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).

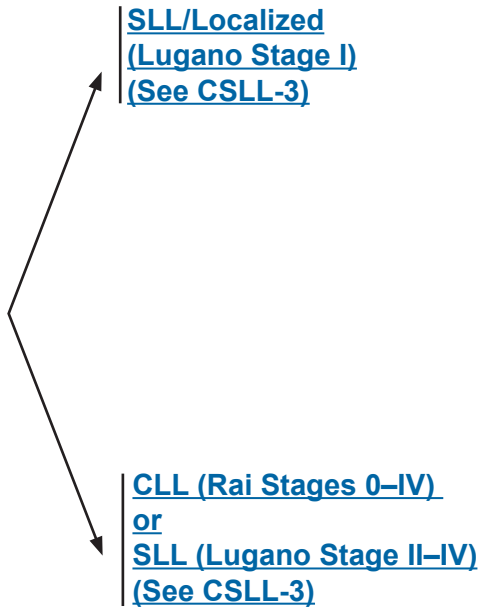
[e] If not available, determination of CD38, CD49d, and ZAP-70 expression by flow cytometry, methylation, or immunohistochemistry may be obtained as surrogate markers for IGHV-mutation status. Evaluation of these markers can be challenging and is not recommended outside the setting of a clinical trial.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

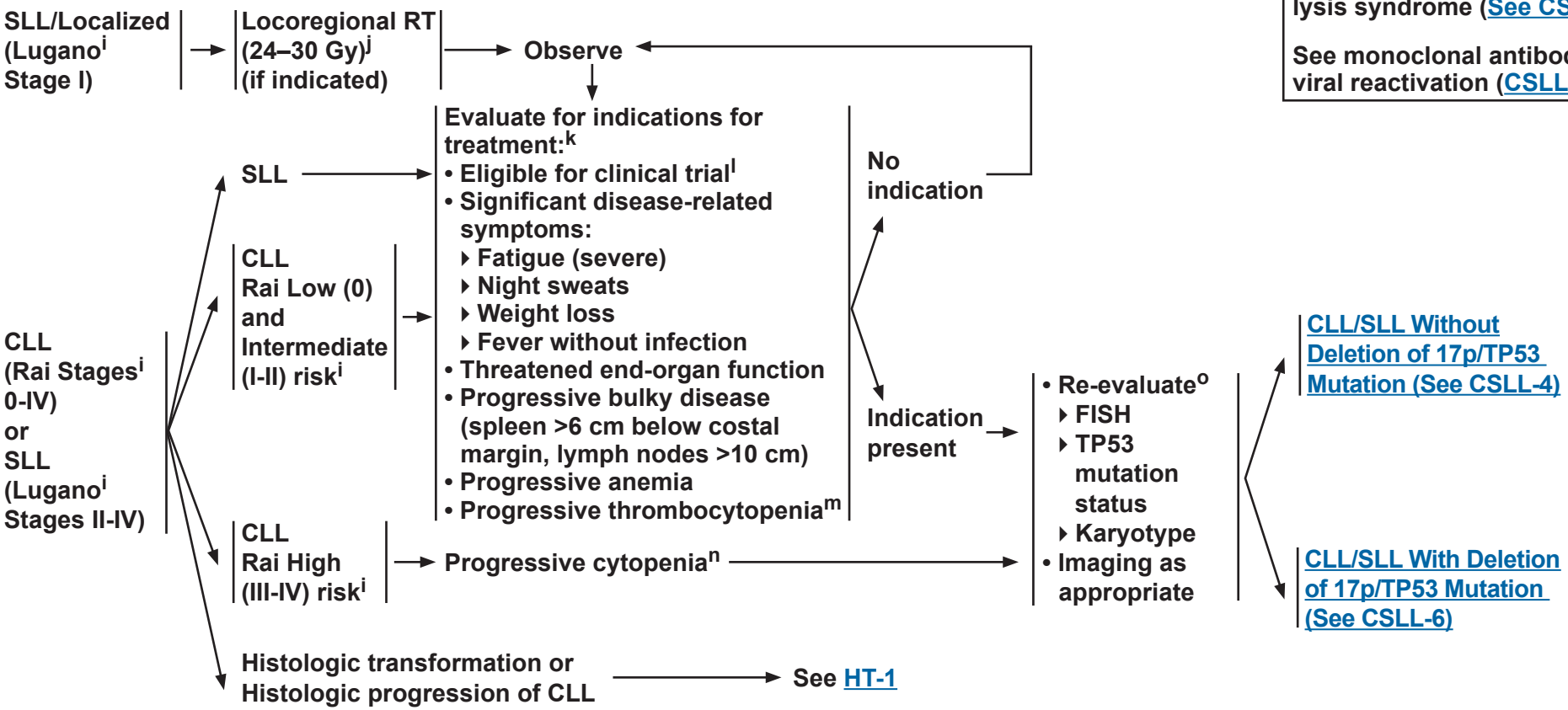
[g]Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous 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.

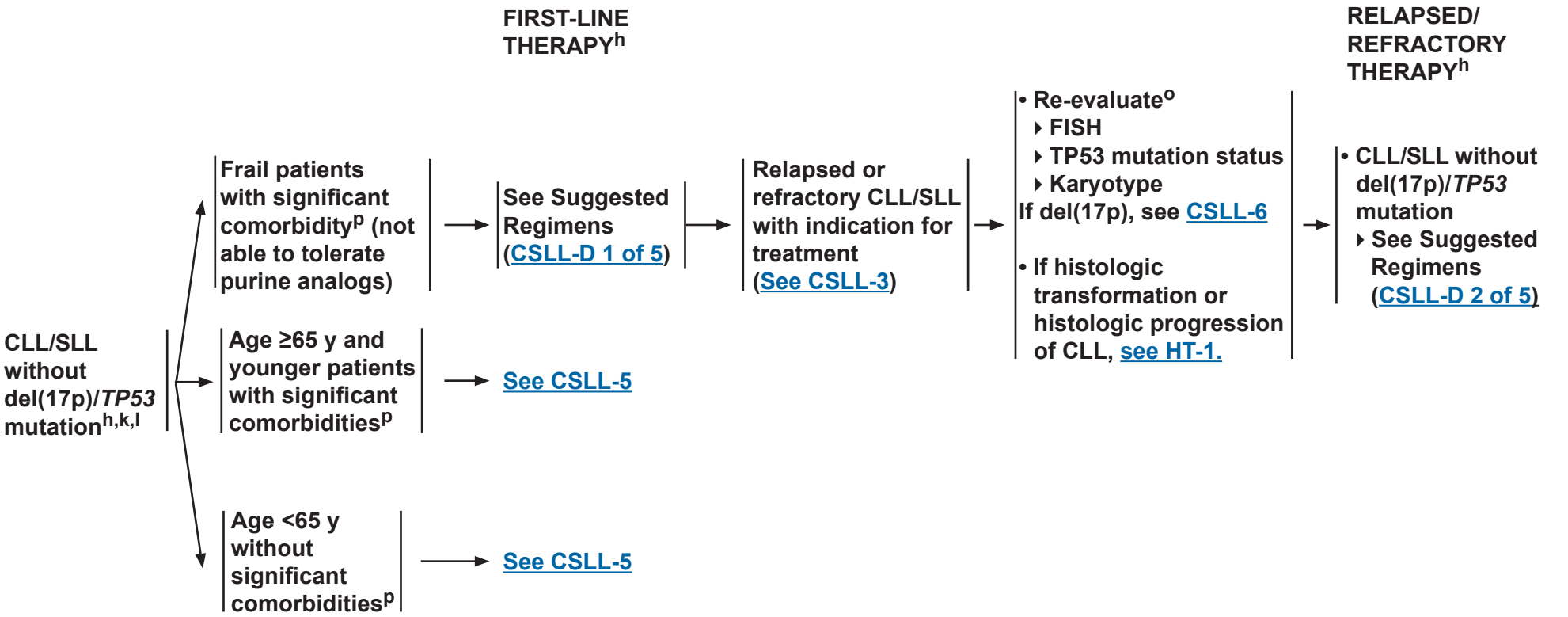
[m] Platelet counts >100,000 cells/mm^3 are typically not associated with clinical risk.

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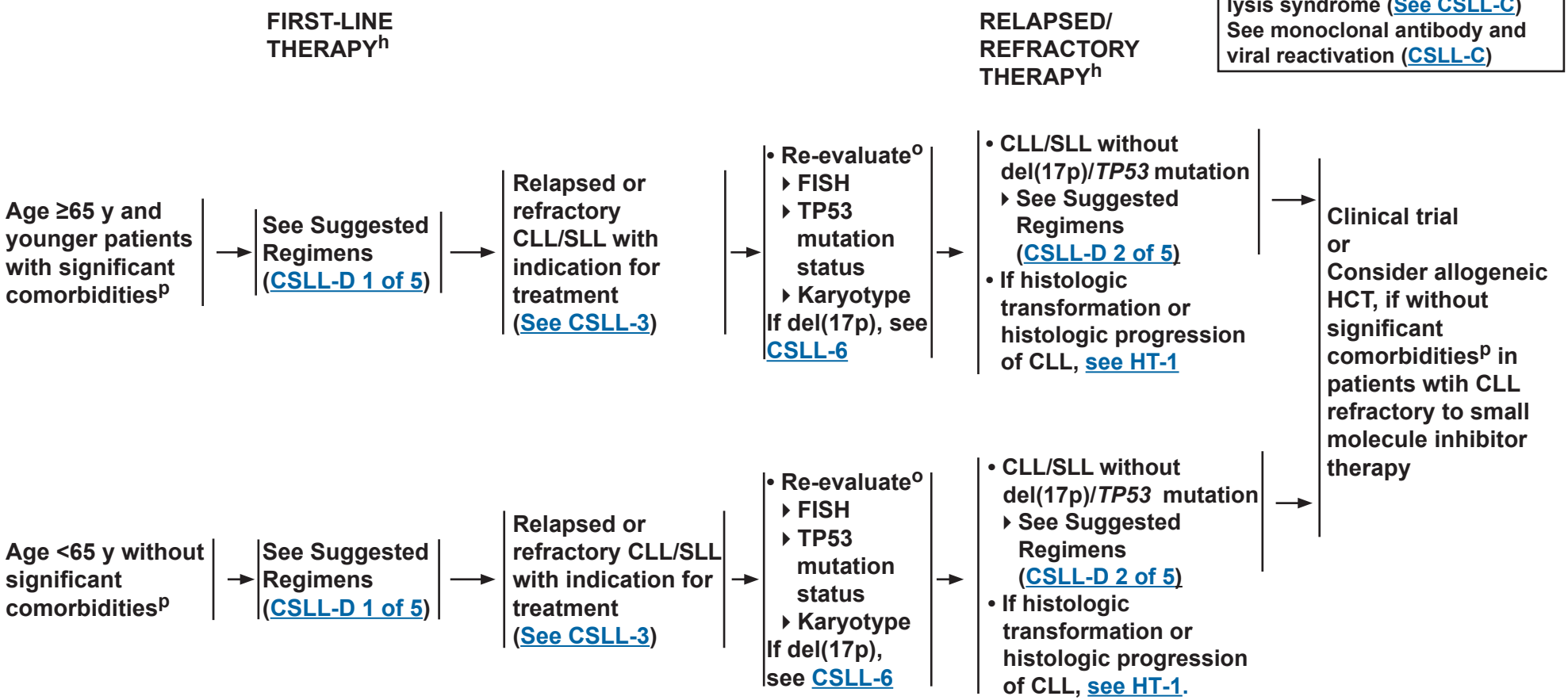
CLL/SLL WITHOUT DELETION OF 17p/*TP53* MUTATION[h,k,l]

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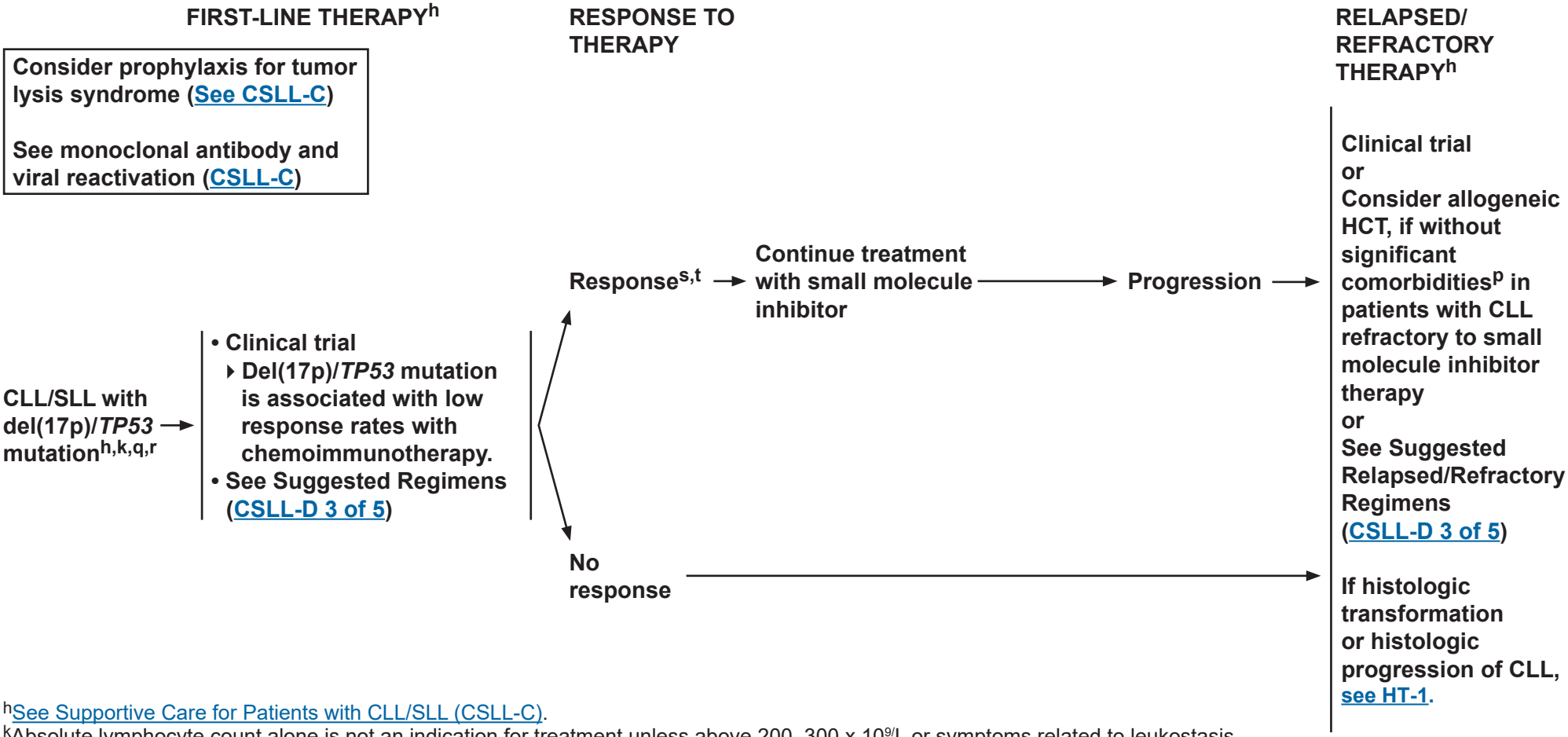
CLL/SLL WITH DELETION OF 17p/*TP53* MUTATION[h,k,q,r]



[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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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 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.

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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

Reprinted with permission. © 2014 American Society of Clinical Oncology. All rights reserved. Cheson B, Fisher R, Barrington S, et al. Recommendations for Initial Evaluation, Staging and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma – the Lugano Classification. J Clin Oncol 2014;32:3059-3067.

[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.

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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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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.

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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)**

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)**

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)**

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

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

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**

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)

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

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)**

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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Continued

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SUGGESTED TREATMENT REGIMENS

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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/μL	Decrease ≥50% over baseline	Increase or decrease <50% over baseline	Increase ≥50% over baseline[b]
Group B Platelet count without growth factors	>100,000/μL	>100,000/μL or increase ≥50% over baseline	>100,000/μL 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/μL	>1500/μL or >50% improvement over baseline	>1500/μL 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.

[a]Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 Guidelines. Blood 2008;111:5446-5456.
[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.

Continued

[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.
  - 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.)
- 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.

Continued

[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]

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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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.

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.

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.

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.

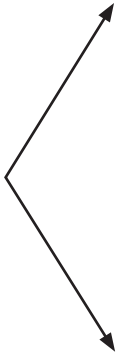
WORKUP

ESSENTIAL:

- History and physical exam 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

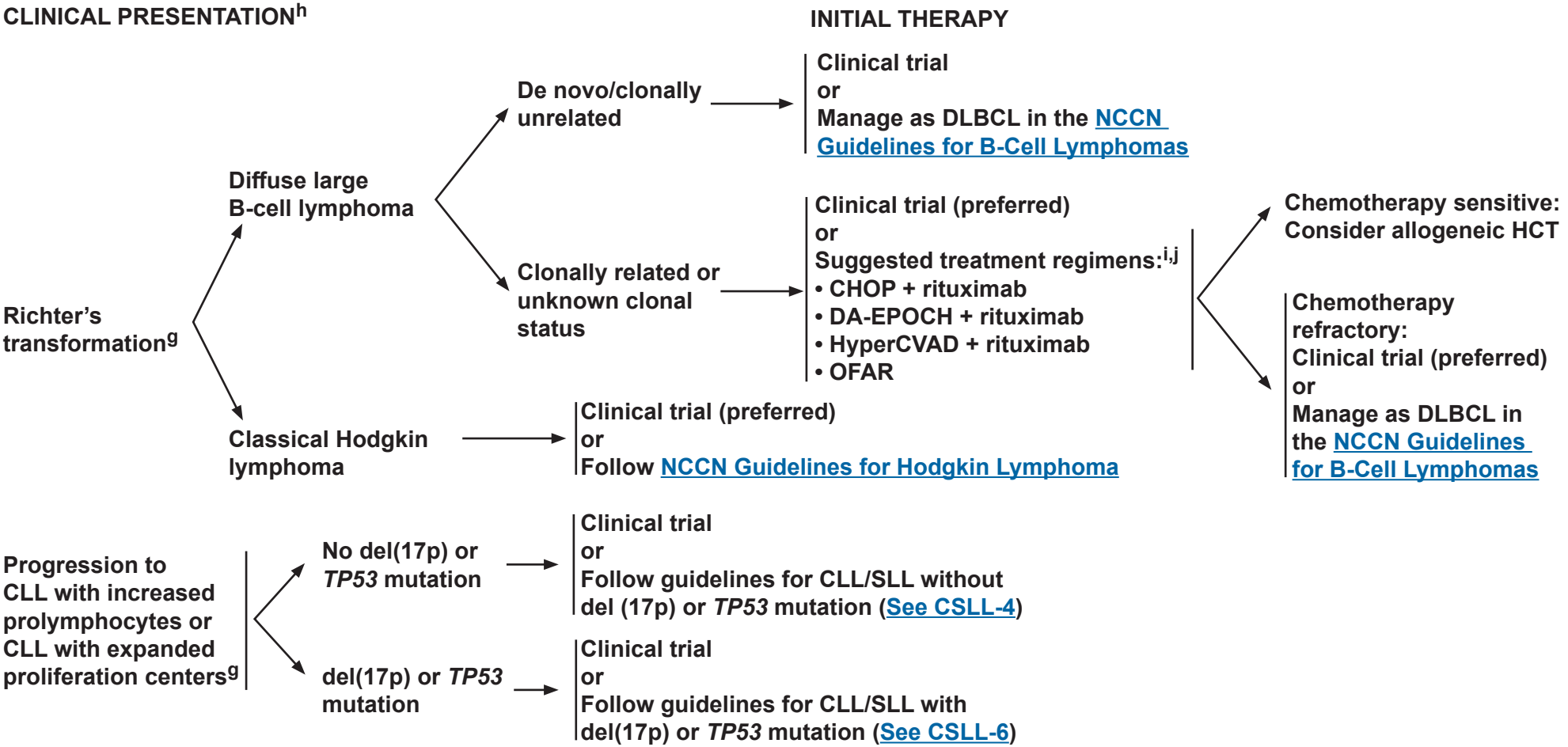


See Richter's Transformation (HT-3)

CLL with Progression (HT-3)

[f]Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, ~~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.

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.



[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.

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.

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.

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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated on 02/21/17

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 noted.

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.

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 2017, an estimated 20,110 people will be diagnosed with CLL in the United States, and an estimated 4,660 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 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 Chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) an electronic search of the PubMed database was performed to obtain key literature in "Chronic Lymphocytic Leukemia" published between July 2015 and October 2016, using the following search terms: chronic lymphocytic leukemia, Richter syndrome, and histologic 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 65 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]

Prognostic Factors

Serum markers such as thymidine kinase and beta-2 microglobulin, flow cytometry-based prognostic parameters (CD38, CD49d, and ZAP-70), immunoglobulin heavy-chain variable region gene (*IGHV)* mutational status, and cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) such as del(13q), del(11q), or del(17p) 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.

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 overall survival (OS) in patients treated with first-line chemoimmunotherapy regimens.[9,10] 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 progression-free survival (PFS) for patients on ibrutinib-based treatment.[10] 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.

Among the flow cytometry based prognostic parameters (CD38, CD49d and ZAP-70), CD49d appears to be the strongest prognostic parameter and is the only one that is independent of FISH and *IGHV*. [11] Expression of CD38 (≥7% of B lymphocytes)[12-17] and/or ZAP-70 (≥20%of B lymphocytes) are associated with shorter PFS and OS outcomes.[18-23] Both CD38 and ZAP-70 positivity correlate with unmutated *IGHV*, and were suggested as potential surrogate markers for *IGHV* mutational status.[12,18,19] 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.[24] Similarly, discordant results between ZAP-70 positivity and *IGHV* mutational status were reported in 20% to 25% of cases.[17,21] 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.[21-23] CD38 and ZAP-70 expressions can be determined using immunohistochemistry (IHC) or flow cytometry. However, standardization and reproducibility of ZAP-70 expression across laboratories remains a challenge. Evaluation of ZAP-70 expression is not recommended outside the context of clinical trials. 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.[25-27]

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.[12,28] In addition, *VH3-21* gene usage was associated with poor outcomes regardless of the mutation status (as defined by percent homology with germline sequence).[29] Unmutated *IGHV* or the use of *VH3-21* was shown to be independent predictors of shorter

treatment-free interval and/or survival outcomes, even when high-risk genomic abnormalities were included in the multivariable regression models.[15,17,30,31] *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. The most common abnormality is del(13q) (55%) as a sole finding, followed by del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%).[32] 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).[32] 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.[17,33] 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.[32] 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.[34] 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.[35-37] Survival estimates are likely outdated as they were determined in the era of chemotherapy or chemoimmunotherapy.

The impact of these cytogenetic abnormalities on clinical outcome has been evaluated in large prospective randomized studies.[17,38,39] In the CLL4 trial, that compared first-line therapy with chlorambucil vs. fludarabine vs. fludarabine and cyclophosphamide (FC), *TP53* loss was found to be the strongest predictor of poor outcomes.[17] 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 OS outcomes.[17] 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.[38] In the phase III randomized CLL8 study that compared FC versus FC combined with rituximab (FCR) as first-line therapy, the presence of *TP53* mutation, del(17p) and unmutated *IGHV* were the strongest predictors of shorter PFS and OS.[39] The median PFS was significantly longer in patients with mutated *IGHV* treated with FCR than those treated with FC (not reached for FCR vs. 41.9 months for FC; $P < .001$), and the 5-year OS rates were 86.3% and 79.8%, 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.[17,40] In the CLL4 trial, the presence of del(17p) in ≥10% or more cells was the strongest predictor of poor outcomes.[17] Patients with del(17p) in ≥10% cells had a response rate of 29% and a median survival of <6 months.[17] 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 1,585 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.[41]

A prognostic nomogram and a more simplified prognostic index has been developed using the routine clinical and laboratory parameters (age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes) to help stratify untreated patients with CLL into three different risk groups (low, intermediate, and high) based on the median survival time, as well as the probability of 5-year and 10-year survival.[42] The estimated median survival was not reached for the low-risk group. The median survival times for intermediate- and high-risk groups were 10 and 5 years, respectively. 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.[42] Several studies have independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in previously untreated patients with CLL, including in patients with early-stage (Rai stage 0) disease.[43,44] In a more recent prognostic nomogram, based on a multivariable model, both traditional clinical and laboratory parameters as well as newer prognostic factors (such as FISH cytogenetics, *IGHV* mutational status, and ZAP-70 expression levels) have been included for estimating the probability of treatment (at 2 and 4 years) and time to first treatment.[45] 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.[45] This nomogram may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention. More recently, an International Group developed a comprehensive prognostic index (CLL-IPI) to stratify patients into 4 risk groups based on OS. In this model, sex, age, ECOG status, del(17p), del(11q), *IGHV* mutation status, serum beta-2 microglobulin, and serum thymidine kinase were identified as independent predictors of OS in newly diagnosed patients.[46]

In the last few years, recurrent mutations in *NOTCH1*, *SF3B1*, and *BIRC3* genes with prognostic implications have been identified.[47-51] *NOTCH1*, *SF3B1*, and *BIRC3* mutations are observed 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.[47,49,51] Messina et al recently reported that recurrent mutations in one or more genes including *TP53* (27.5%), *NOTCH1* (24.1%), *SF3B1* (18.9%), and *BIRC3* (15.5%) are present in more than 70% of patients with CLL refractory to fludarabine.[52] Rossi et al have proposed an integrated prognostic model including *NOTCH1*, *SF3B1*, and *BIRC3* mutations along with the cytogenetic abnormalities identified by FISH to classify patients into 4 distinct prognostic subgroups: high-risk (*TP53* and/or *BIRC3* abnormalities); intermediate-risk (*NOTCH1* and/or *SF3B1* mutations and/or del11q); low-risk (trisomy 12 and wild-type for all genetic lesions), and very low-risk (del13q only).[53] The 10-year survival rates for the 4 subgroups were 29%, 37%, 57%, and 69%, respectively.

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.[54-56] 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.[55] 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.[56] 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.[37] *NOTCH1* mutation was also independently associated with Richter's transformation.[57,58] In a study based on data from a large multicenter series of newly diagnosed patients with CLL, the cumulative probability of developing Richter's transformation was significantly higher for patients with *NOTCH1* mutations at diagnosis compared to those without the mutation (45% vs. 5% at 15 years; $P < .001$).[57]

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, treatment initiation or selection of treatment options should not be driven by these factors. The impact of these mutations relative to treatment with newer targeted therapies is uncertain. Moreover, in the general clinical practice setting, prognostic factors should not determine treatment choices, with the exception of del(17p) or del(11q).

Response Criteria

The National Cancer Institute-sponsored Working Group (NCI-WG) on CLL published guidelines for the diagnosis and management of CLL in 1988 and 1996, primarily to facilitate consistency in the design and conduct of clinical trials. Most clinical trials of CLL reporting response outcomes have, until very recently, utilized the response criteria set forth in the 1996 NCI-WG guidelines.[59] In 2008, the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) revised the NCI-WG guidelines 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 on 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. For a complete response (CR), all of the following criteria must be met (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. For a partial response (PR), at least 2 of the following criteria must be met for at least 2 months duration: at least 50% reductions from baseline in peripheral blood lymphocyte counts, 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 (ibrutinib and idelalisib).[60] 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.[61]

The use of small molecule inhibitors (ibrutinib and idelalisib) targeting kinases involved in a number of critical signaling pathways 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.[62,63] 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.[62] Considering these findings, for patients receiving idelalisib and ibrutinib, the revised response criteria recently 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).[60]

Minimal residual disease (MRD) negativity determined in the peripheral blood after the end of treatment is emerging as an important predictor of treatment efficacy.[64,65] In the combined analysis of two randomized phase III studies of the GCLLSG (CLL8 and CLL10), among patients who achieved CR and PR, PFS was longer for those with MRD-negative CR and MRD-negative PR (61 months and 54 months, respectively) than those with MRD-positive CR and MRD-positive PR (35 months and 21 months, respectively).[64] 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 FCR chemoimmunotherapy also correlated with PFS.[65] These results support the use of MRD for response evaluation.

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, which is established by flow cytometry quantification.[3] 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-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.[66] 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.[67]

The guidelines now include an initial stratification between CLL/SLL and MBL (absolute B-lymphocyte count of less than 5000/mm^3, lymph nodes less than 1.5 cm, and no thrombocytopenia or anemia). Observation is recommended for all individuals with MBL. The diagnosis of CLL requires the presence of at least 5000 monoclonal B-lymphocytes/mcl (5 x 10^9/L) in peripheral blood and the clonality of B cells should be confirmed by flow cytometry. 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.

Adequate immunophenotyping is essential to establish the diagnosis of CLL/SLL. 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. Cell surface markers for flow cytometric studies should include kappa/lambda, CD19, CD20, CD5, CD23, and CD10. Flow evaluation for cyclin D1 or FISH analysis for t(11;14) should also be included in the workup to rule out mantle cell lymphoma (MCL).

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.

The typical immunophenotype for CLL/SLL is CD5+, CD10-, CD19+, and CD20 dim, surface immunoglobulin dim, CD23+, CD43 +/-, and cyclin D1-. Distinguishing CLL/SLL from 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. Stimulated cytogenetics or FISH analysis for t(11;14) can help to distinguish MCL from CLL, and should be performed if flow cytometry alone is used to evaluate immunophenotype. FISH for the detection of del(11q), del(13q), trisomy 12, del(17p), stimulated metaphase karyotype, and molecular genetic analysis (by polymerase chain reaction or sequencing) to detect *IGHV* mutation status and *TP53* mutations can provide useful prognostic information and may guide selection of therapy.

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 chromosomal abnormalities that may have prognostic significance. However, FISH can only detect abnormalities specific to the probes utilized. Cytokine or CpG oligonucleotide stimulation was utilized to enhance metaphase analysis.[68] Recent studies demonstrated that stimulation with CpG oligonucleotide and interleukin-2 is more effective than that with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) for the detection of chromosomal abnormalities in CLL.[69,70] 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 FISH and are reproducible among different cytogenetic laboratories.[71] However, the use of CpG stimulation for CLL cytogenetics is not yet universally available. 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.

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.[42,72] 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.[73,74] Bone marrow biopsy ± aspirate could be useful in ceratin circumstances prior to initiation of treatment.

Treatment Options

During the last several decades, therapeutic options for CLL have evolved significantly. The advent of immunomodulating agents (eg, lenalidomide) and CD20 (rituximab, obinutuzumab, and ofatumumab) and CD52 (alemtuzumab) monoclonal antibodies (mAbs) has led to the development of new and effective combination chemoimmunotherapy regimens. More recently, novel small molecule inhibitors targeting kinases involved in a number of critical signaling pathways (eg. Bruton's tyrosine kinase [BTK], phosphatidylinositol 3-kinase [PI3K] and spleen tyrosine kinase [SYK]) and a small molecule inhibitor of BCL-2 family of proteins with potent anti-leukemia therapeutic activity have demonstrated promising results for the treatment of patients with CLL/SLL.[75,76] A large number of ongoing clinical trials are evaluating novel combination regimens including drugs with different mechanism action.

First-line Therapy

Fludarabine with concurrent or sequential administration of rituximab was evaluated in the CALGB 9712 study in untreated patients with CLL.[38,77] 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).[77] 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%.[38] 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.[78]

Fludarabine, cyclophosphamide and rituximab (FCR) regimen results in high response rates and improved OS in specific subgroups of fit patients with previously untreated CLL, especially in those with mutated IGHV.[39,79] In a phase II study of 300 patients with previously untreated CLL, at a median follow-up of 12.8 years, the ORR was 95% (72% CR).[79] The median PFS was 6.4 years and the overall 12.8-year PFS rate was 30.9% (53.9% for patients with mutated *IGHV* and 8.7% for patients with unmutated *IGHV*). MRD-negativity was achieved in 50.7% of patients with mutated *IGHV,* with a PFS rate of 79.8% at 12.8 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. 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 FCR (n = 408) or FC (n = 409) regimen.[39] The FCR regimen resulted in higher ORR (90% vs. 80%; *P* < .001) and CR rate (44% vs. 22%; *P* < .001) compared with FC. With a median follow-up of 5.9 years, the median PFS was 56.8 months for FCR and 33 months for FC (*P* < .001); the median OS was not reached for FCR and was 86.0 months for FC (*P* = .001).[39] FCR was associated with a statistically significant survival benefit compared to FC in patients <65 years (5-year OS rates were 80.9% and 69.2%, respectively; *P* = .002). The corresponding 5-year OS rates were 73.9% and 61.6%, 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 (16.6% vs. 8.8%; *P* = .007).

Pentostatin has also been evaluated as part of first-line chemoimmunotherapy regimens.[80-82] In a phase II trial, pentostatin, cyclophosphamide, and rituximab (PCR) resulted in an ORR of 91% (41% CR) in patients with poor-risk prognostic factors (eg, high-risk Rai stage, unmutated *IGHV*, and cytogenetic abnormalities detected by FISH), with a median PFS of approximately 33 months.[80] PCR regimen was also less myelotoxic than FCR regimen. In a subsequent study that investigated the possibility of using a higher dose of pentostatin (to reduce the toxicity of the PCR regimen by omitting cyclophosphamide) in previously untreated patients (n = 33), the combination of higher dose pentostatin with rituximab (PR) resulted in an ORR of 76% (CR 27%).[81] However, the response rate was lower than that observed with PCR and the median treatment-free survival was also decreased (16 months vs. 30 months for PCR), suggesting that cyclophosphamide is an important component of the chemoimmunotherapy regimen. In a community-based multicenter phase III randomized trial (n = 184) that compared the safety of PCR (using higher dose pentostatin) with the FCR regimen in previously untreated (80% of patients) or minimally pretreated patients, the ORR with PCR and FCR were similar (49% vs. 59%), with a lower CR rate in the PCR group (7% vs. 14%; *P* = .04).[82] 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.[82] Overall, the PCR regimen did not appear to provide an advantage over FCR in terms of efficacy or toxicity.

Bendamustine, an alkylating agent, with a low cross-resistance with other alkylating agents was evaluated as first-line monotherapy and in combination with rituximab.[83-86] 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 (21.0% vs. 10.8%), median PFS (21.2 months vs. 8.8 months; $P < .0001$), and time to next treatment (31.7 months vs. 10.1 months; $P < .0001$) compared to chlorambucil.[83] No differences in OS were observed between the two groups. The higher response rates and PFS benefit with bendamustine was 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 a multicenter phase II trial (CLL2M study) from the GCLLSG, bendamustine and rituximab (BR) induced high response rates (ORR, 88%; CR, 23%) in previously untreated patients (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).[84] After a median observation time of 27 months, the median PFS for all patients was 34 months, and OS rate was 90.5%. The BR regimen appeared to have limited activity in a small subgroup of patients (n = 8) with del(17p), resulting in an ORR of 37.5% (all partial remissions), with a median PFS of only 8 months.[84] Thrombocytopenia (22%), neutropenia (20%), anemia (20%), allergic/infusion reactions (9%), and infections (8%) were the most common grade 3 or 4 toxicities.

The final analysis of the CLL10 study that compared BR with FCR as first-line therapy for CLL without del(17p) in fit patients (n = 567; CIRS score ≤ 6, creatinine clearance > 70 ml/min) confirmed the superiority in PFS with FCR over bendamustine plus rituximab in patients ≤65 years, without significant comorbidities.[85] The median age was 61.6 years for all patients, but significantly higher proportion of patients were > 65 years in the BR arm (39% vs 30%). After a median follow-up of 37.1 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 (55.2 months vs. 41.7 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 53.6 months and 38.5 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 55.4 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. The updated results of the study confirmed that BR is also associated with a decreased risk of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).[87] After a median follow-up of 58.2 months, the incidences of secondary AML and MDS were 3% and 1% in FCR and BR arms, respectively. The results of the study confirm that FCR remains the standard first-line therapy for untreated CLL in fit patients and particularly for patients with mutated *IGHV*. BR is an alternative treatment option for elderly fit patients or patients with previous infections.

An ongoing phase III randomized trial is comparing rituximab and chlorambucil (R-chlorambucil) and BR as first-line or second-line therapy in patients with CLL who are not candidates for fludarabine-based chemoimmunotherapy due to older age or the presence of comorbid conditions.[86] In the interim analysis of this trial, (126 evaluable patients; 58 patients treated with BR; 68 patients treated with R-chlorambucil; median age 74 years, range 44–91), at the median

follow-up of 24 months, the ORR was 91% in the BR group (CR in 24%) and 86% (CR in 9%) in the R-chlorambucil group among the patients who received first-line therapy.[86] The median PFS was significantly longer for patients in the BR group than for those in the R-chlorambucil group (40 months vs. 30 months; *P* = .003), but the median OS was not significantly different (44 months vs. not calculable). The incidence of adverse events was similar between treatment groups (98% for BR and 97% for R-chlorambucil) but the incidence of grade 3 adverse events was higher for BR compared to R-chlorambucil (75% and 64%, respectively).

High-dose methylprednisolone (HDMP) in combination with rituximab has demonstrated activity in a small cohort of patients with previously untreated CLL with poor-risk factors (n = 28).[88] The median age was 65 years and a large proportion of patients had poor-risk factors at baseline (eg, high-risk Rai stage in 48%; unmutated *IGHV* in 57%; cytogenetic abnormalities in 39%). Treatment with HDMP + rituximab resulted in 96% ORR with CR in 32% of patients. At a median follow-up of 36 months, the median PFS was 30.5 months and OS rate was 96%.[88] In the small subgroup of patients aged >70 years (n = 8), all patients responded and 3 patients achieved a CR (38%).

Lenalidomide, an immunomodulating agent, has been evaluated as first-line therapy in several studies both as monotherapy and in combination with rituximab.[89-91] Long-term follow-up data from a phase II study that evaluated lenalidomide (initial dose of 5 mg daily, with dose escalation up to 25 mg; given daily for 28 days of 28-day cycle) in previously untreated patients 65 years or older (n = 60) showed that 58% of patients achieved responses lasting 36 months or longer, and 25 of these patients were still on therapy; no deaths occurred among the long-term responders.[89] The median time to treatment failure was not reached and the OS rate was 82%. Long-term responders had lower baseline plasma levels of beta-2-microglobulin and were also more likely to have trisomy 12 and less likely to have del(17p). All of the long-term responders (n = 35) experienced neutropenia (grade 3 or 4 in 12 patients; 34%) neutropenia during the first 12 months of therapy, which was later resolved in 29 patients (83%), mostly through dose reduction. In another phase II study in patients with previously untreated CLL (n = 25), after an extended median follow-up of 53.2 months, lenalidomide (initial dose 2.5 mg daily, with dose escalation up to 10 mg daily; given 21 days of 28-day cycle) resulted in an ORR of 72% (20% CR).[90] The 3-year PFS and OS rates were 65% and 85%, respectively. Myelosuppression was common during the first year of treatment (grade 3–4 neutropenia and thrombocytopenia were reported in 76% and 28% of all patients, respectively) and the rate of recurrence decreased over long-term treatment. TFRs occurred in 88% of patients but were all grade 1 or 2 events. Fatigue (76%), rash (60%), muscle cramping (40%), and diarrhea (40%) were the other most common non-hematologic toxicities. Lenalidomide (initial dose 2.5 mg daily, with dose escalation up to 10 mg daily) in combination with rituximab (dose escalated to 375 mg/m^2 cycle 1; 375 mg/m^2 weekly for 4 weeks) was evaluated in a multicenter phase II study of the CLL Research Consortium in previously untreated patients with CLL (n = 69; age <65 years, n = 40; age ≥65 years, n = 29).[91] Only 59% of the older patient group completed the planned 7 cycles of therapy compared with 88% of patients younger than 65 years. TFR (predominantly grade I-II) occurred in 83% of patients aged <65 years and in 66% of patients aged ≥65 years. The most common grade 3 or 4 toxicity was neutropenia, which was reported in 76% of patients. Among evaluable patients (n = 65), the ORR was 95% (20% CR and 20% nodular PR) in patients younger than 65 years (n = 38) and the ORR in patients 65 years or older (n = 27) was 79% (10% CR). After a median follow-up of more than 20 months, the median PFS was 19

months and 20 months, respectively, for the younger and older cohort; median OS was not reached in either arm.[91] A randomized phase III study (ORGIN trial) evaluating monotherapy with lenalidomide vs. chlorambucil as initial therapy for CLL in elderly patients older than 65 years was recently halted by the FDA due to concerns for increased risk of death in the lenalidomide arm vs. chlorambucil arm.[92] Evaluation of lenalidomide as initial therapy for elderly patients with CLL should occur only in the context of a clinical trial based on these results.

Rituximab in combination with chlorambucil has resulted in reasonable ORR and CR rates of 82.5% to 84% and 10% to16.5%, respectively in patients with previously untreated CLL.[93,94] However, in the CLL11 trial (discussed below) that compared chlorambucil in either combination with rituximab or obinutuzumab, there was a clinically meaningful improvement in PFS with a trend towards improved OS in patients treated with obinutuzumab + chlorambucil versus rituximab + chlorambucil.[95,96] Thus, first-line treatment with rituximab and chlorambucil should be reserved for patients who cannot tolerate obinutuzumab.

Obinutuzumab is a glycoengineered, humanized, type II antibody targeted against CD20 that had demonstrated activity in patients with untreated CLL.[95-97] The results of the CLL 11 study established obinutuzumab plus chlorambucil as the new standard of care for both elderly patients and for patients with comorbidities lacking del(17p).[95,96] In this study, 781 patients with comorbid conditions (defined as CIRS score >6 or an estimated creatinine clearance [CrCl] of 30 to 69 mL/min) were randomized to receive chlorambucil (n = 118), obinutuzumab plus chlorambucil (n = 333), or rituximab plus chlorambucil (n = 330).[95] The combination of obinutuzumab plus chlorambucil and rituximab plus chlorambucil resulted in significant improvement in the median PFS compared to chlorambucil alone (26.7 months, 16.3 months, and 11.1.months, respectively, for obinutuzumab plus chlorambucil, rituximab plus chlorambucil, and chlorambucil alone; $P < .001$).[95] The survival benefit was seen in all of the subgroups except in patients with del(17p). After the median observation time of 39.0 months, obinutuzumab plus chlorambucil significantly prolonged median PFS (28.7 months vs. 15.7 months; $P < .001$), and median time to next treatment (51 months vs. 38.2 months; $P < .0001$) compared to rituximab plus chlorambucil. There was also a trend towards OS benefit for obinutuzumab.[96] The most frequent grade 3 or higher toxicities with obinutuzumab-chlorambucil included neutropenia (35%), infusion-related reactions (21%), thrombocytopenia (11%), and infections (11%). Neutropenia (28%) and infections (14%) were the most frequent grade 3 or higher toxicities associated with rituximab plus chlorambucil. Based on the results of this study, obinutuzumab in combination with chlorambucil was FDA approved for the treatment of untreated CLL/SLL. The efficacy of obinutuzumab monotherapy at two different doses (1,000 mg vs. 2,000 mg) in 80 patients with intact organ function and ECOG PS <3 was evaluated in a phase II study (GAGE).[97] 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.[97] 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 obinutuzumab monotherapy in patients with untreated CLL.

Ofatumumab, a fully human CD20 monoclonal antibody, initially approved for the treatment of CLL refractory to fludarabine and alemtuzumab. A multicenter open-label phase III study

(COMPLEMENT 1) evaluated ofatumumab as a first-line treatment for patients with untreated CLL who were considered inappropriate for fludarabine-based therapy due to advanced age and/or co-morbidities; 447 patients were randomized to ofatumumab plus chlorambucil vs. chlorambucil monotherapy.[98] After a median follow-up of 29 months, the median PFS was significantly longer for ofatumumab plus chlorambucil compared to chlorambucil monotherapy (22.4 months vs. 13. 1 months; *P* < .001).[98] The median OS was not reached in both arms. Ofatumumab plus chlorambucil also resulted in higher ORR (82% vs 69%, P =.001) and superior CR rate (12% vs 1%) compared to chlorambucil alone. Based on the results of this study, the FDA approved ofatumumab plus chlorambucil for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.

Alemtuzumab, a humanized CD52 monoclonal antibody, was initially approved for fludarabine-refractory CLL and has since shown activity as a first-line treatment for patients with CLL, both as a monotherapy and in combination regimens.[99-101] In an international, multicenter randomized phase III study (CAM307), previously untreated patients with CLL (n = 297) were randomized to receive alemtuzumab or chlorambucil.[100] Alemtuzumab resulted in a significantly higher ORR (83% vs. 55%; *P* < .0001) and CR rate (24% vs. 2%; *P* < .0001) than chlorambucil; in addition, a modest but statistically significant benefit in PFS was observed with alemtuzumab compared with chlorambucil (median 15 months vs. 12 months; *P* = .0001). In the small subgroup of 21 patients with del(17p), alemtuzumab showed higher ORR (64% vs. 20%) and longer median PFS (11 months vs. 2 months). 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.[100] Alemtuzumab was associated with higher incidence of infusion-related events, cytomegalovirus (CMV) infections, and grade 3 or 4 neutropenia (41% vs. 25%) compared with chlorambucil. While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Alemtuzumab is not recommended as a first-line treatment option except for del(17p) CLL/SLL when ibrutinib is not deemed to be appropriate.

Ibrutinib, an irreversible inhibitor of BTK, initially approved for relapsed or refractory CLL (in patients who have received at least one previous therapy), was also evaluated in patients with untreated CLL or SLL including those with del(17p).[102-106] The 5-year follow-up data from the multicenter phase Ib/II study that included 31 patients ≥65 years with untreated CLL or SLL confirmed that ibrutinib induces very durable responses across all subgroups, including patients ≥ 65 years with untreated CLL or SLL and those with del17p, del11q, or unmutated *IGHV*.[103] After a median follow-up of 5 years, ibrutinib (420 mg) resulted in an ORR of 84% (29% CR). The median PFS was not reached and the estimated PFS rate at 60 months was 92%. The responses were independent of the presence of high-risk features; however, the number of patients with del(17p), del(11q), trisomy 12 or elevated beta-2-microglobulin was small in this study. In another phase II trial that included 35 treatment-naïve patients with del(17p) treated with ibrutinib (≥18 years; 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 PR and 42% of patients had PR with lymphocytosis) and the estimated OS at 24 months was 84%.[104] 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. 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).[105] After a median follow-up of 28.6 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% for patients treated with ibrutinib and chlorambucil, respectively.[106] Ibrutinib was approved for first-line therapy for all patients, although the efficacy of ibrutinib as first-line therapy in patients <65 years without del(17p) has not been established in randomized clinical trial.

First-line Consolidation Therapy

The CLLM1 study demonstrated the feasibility and efficacy of lenalidomide maintenance after first-line therapy.[107] In this study, 89 patients with a poor outcome after first-line chemoimmunotherapy (those who achieved at least a PR to first-line chemoimmunotherapy 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 = 69) or placebo (n = 20). After a median observation time of 17.7 months, the median PFS in the placebo arm was 14.6 months, and was not reached in the lenalidomide arm. The incidences of treatment-related adverse events such as neutropenia (30.4% vs 3.4%), gastrointestinal disorders (55.4% vs 27.6%), nervous system disorders (30.4% vs 13.8%), respiratory disorders (35.7% vs 13.8%) and skin disorders (60.7% vs 27.6%) were more frequent with lenalidomide.

Relapsed or Refractory Therapy

The current standards of care for relapsed or refractory CLL or SLL are ibrutinib, idelalisib, and idelalisib with rituximab and venetoclax ± rituximab for relapsed/refractory del(17p) CLL/SLL.

Ibrutinib has remarkable monotherapy activity with favorable toxicity profile in patients with relapsed or refractory CLL.[108-110] In the phase III randomized study (RESONATE), 391 patients with previously treated CLL were randomized to monotherapy with ibrutinib (420 mg once daily) or ofatumumab.[108] The majority of patients had advanced stage disease and high-risk features including del(17p), del(11q), or beta-2 microglobulin (>3.5 mg/L). At a median follow-up of 9.4 months, ibrutinib significantly prolonged PFS (median not reached vs. 8.1 months for ofatumumab) and OS (HR for death in the ibrutinib group was 0.43; *P* = .005; 57% reduction in the risk of death). Among patients with del(17p), median PFS was not reached with ibrutinib, compared with a median PFS of 5.8 months with ofatumumab.[108] At 12 months, the OS rate was 91% and 81%, respectively, for ibrutinib and ofatumumab. The ORR was also significantly higher with ibrutinib (42% vs. 4%; *P* < .001). The most frequent nonhematologic adverse events were mild (Grade 1-2) diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. The updated results of this study also confirmed that ibrutinib significantly improved ORR, PFS and OS compared to ofatumumab in patients with CLL/SLL who had received at least one prior therapy [109] With a median follow-up of 16 months, the ORR (90% vs. 25%; *P* < .0001), median PFS (not reached vs. 8.1 months for ofatumumab; *P* < .0001) and OS rates (18-month OS rates were 85% and 78%, respectively) were significantly better for ibrutinib. The results of the phase II study (RESONATE-17) further confirmed the safety and efficacy of ibrutinib in 145 patients with relapsed or refractory del (17p) CLL.[110] At a median

follow-up of 11.5 months, the ORR (as assessed by the independent review committee) was 83%. In an extended analysis with a median follow-up of 27.6 months, the investigator-assessed ORR and the 24-month PFS and OS rates were 83%, 63%, and 75%, respectively.[110]

Idelalisib (the isoform-selective oral inhibitor of PI3K-delta) has demonstrated promising clinical activity in phase I-II studies in patients with relapsed or refractory CLL or SLL, both as monotherapy and in combination with rituximab.[111-113] In the multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with either idelalisib (150 mg) or placebo.[111] The majority of the patients (78%) were 65 years or older, 40% had moderate renal dysfunction (creatinine clearance, <60 mL/min), 35% had poor bone marrow function (grade 3 or higher cytopenias), and 85% had a score CIRS score >6. At the first planned interim analysis, the study was stopped early owing to the overwhelming efficacy of idelalisib plus rituximab.[111] At 24 weeks, the PFS rate was 93% and 46% in the idelalisib group and placebo group, respectively. Among patients with relapsed CLL with co-existing conditions, idelalisib plus rituximab significantly improved ORR (81% vs. 13%; *P* < .001), PFS (not reached in the idelalisib group vs. 5.5 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.[114] Idelalisib plus rituximab also retained efficacy in patients with high-risk features such as del(17p) or *TP53* mutations; unmutated *IGHV*, ZAP70, and CD38 expression; and beta-2 microglobulin (>4 mg/L).[112] 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.[113] 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 3.7 months and 11.4 months, respectively.

Idelalisib monotherapy is approved for the treatment of relapsed SLL in patients who have received at least two prior systemic therapies. Idelalisib in combination with rituximab is approved for the treatment of relapsed CLL in patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥ 3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents). Due to infection-related toxicity and deaths seen with idelalisib in previously untreated CLL in phase III clinical trials, it should not be used in first-line. Prescribers should be aware of this increased risk for infections in patients with relapsed/refractory CLL. Infection prophylaxis for HSV, PJP, and routine monitoring for CMV reactivation are recommended for patients on idelalisib.

Venetoclax, a small-molecule BCL2 inhibitor that induces CLL cell apoptosis, has demonstrated activity in relapsed or refractory CLL.[115,116] 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.[115] Venetoclax resulted in high ORR (>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. Based on the results of this study, venetoclax was approved for the treatment of relapsed or refractory del(17p) CLL. Venetoclax has also shown promising activity in patients with relapsed or refractory CLL who have failed or are intolerant to ibrutinib or idelalisib.[116] In a phase II study of 64 patients with relapsed or refractory CLL after prior treatment with ibrutinib (Arm A; n = 43; 39 patients refractory to ibrutinib) or idelalisib (Arm B; n = 21; 14 patients refractory to idelalisib), venetoclax resulted in an ORR of 70% (Arm A) and 48% (Arm B).[116] In the subset of patients with CLL refractory to ibrutinib or idelalisib, the ORR were 67% (26 of 39 patients in Arm A) and 57% (8 of 14 patients in Arm B) respectively. The estimated 12-month PFS and OS for all patients were 72% and 90% respectively. The median PFS and OS was not reached at the time of the analysis. 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 tumor lysis syndrome (TLS) is recommended to mitigate the risk and frequency of TLS in patients receiving venetoclax.[115,117] Neutropenia can be a longer-term toxicity requiring growth factor support and/or venetoclax dose adjustment. Venetoclax in combination with rituximab is also active in patients with relapsed or refractory CLL/SLL resulting in an ORR of 86% (51% CR) with an estimated 2-year PFS rate of 82%.[118]

The FCR regimen was shown to induce high response rates in the relapsed or refractory disease setting.[119,120] The phase III randomized REACH trial compared 6 cycles of FCR with 6 cycles of FC in patients with CLL at first relapse (n = 552; patients were excluded if they had received prior FC regimen or prior rituximab and, moreover, patients were required to be fludarabine sensitive).[119] After a median follow-up time of 25 months, 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. 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.[119] 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).[120] 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 19.5% of cycles. Pneumonia or sepsis was reported in 16% of patients. The subgroup of patients with fludarabine-refractory disease (n = 54) had 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; $P < .05$) was also significantly decreased among patients with fludarabine-refractory CLL.[120] In addition, the subgroup of patients (n = 20) with chromosome 17 abnormalities (based on standard karyotyping) had the worse outcomes with an ORR of 35% (no CR), median PFS of 5 months, and median survival of only 10.5 months. The investigators concluded that the patients most appropriate for therapy with FCR were those who were fludarabine sensitive, with no chromosome 17 abnormalities, and with fewer prior therapies (<4 prior regimens).[120]

Pentostatin has also been evaluated in patients with fludarabine-refractory disease. In a small series of patients with relapsed or refractory CLL, both PC and PCR have resulted in similar ORR (74% and 75%, respectively) among patients with fludarabine-refractory disease.[121,122] However, based on a historical retrospective comparison, the median duration of response (25 months vs. 7 months) and median survival (44 months vs. 16 months) were longer with the PCR regimen compared with the PC regimen, suggesting that cyclophosphamide is an important component of the PCR regimen even for patients with relapsed or refractory CLL.[121]

Oxaliplatin, fludarabine, cytarabine, and rituximab (OFAR) was shown to have significant activity in relapsed or refractory CLL (including patients with high-risk features such as del(17p) or del(11q)) and Richter's transformation.[123,124] In a phase I-II trial of patients with fludarabine-refractory CLL (n = 30) and those with Richter's transformation (n = 20), OFAR resulted in an ORR of 50% and 33%, respectively, in patients with Richter's transformation and fludarabine-refractory CLL.[123] The median response duration was 10 months. The ORR in the subgroup of patients aged 70 years or older (n = 14) was 50%. In addition, responses were achieved in seven (35%) of 20 patients with del(17p) and two (29%) of seven patients with del(11q).[123] In the subsequent phase I-II study (67 patients with relapsed or refractory CLL and 35 patients with RS), a modified OFAR regimen with reduced-dose cytarabine also resulted in an ORR of 38.7% (6.5% CR) in patients with RS and 50.8% (4.6% CR) in those with relapsed or refractory CLL. The median survival durations were 6.6 and 20.6 months, respectively.[124] Cytopenias were the most common hematologic toxicities. Allogeneic stem cell transplant (SCT) as post-remission therapy in patients treated with modified OFAR was associated with prolonged survival.[124]

In a phase II trial of GCLLSG, the combination of bendamustine and rituximab resulted in an ORR of 59% (CR rate 9%) in patients with relapsed CLL (n = 78; median 2 prior therapies).[125] The ORR among the subgroup (n = 22) with fludarabine-refractory disease was 45.5%. After a median follow-up of 24 months, the median PFS and OS for all patients were 15 months and 34 months, respectively. Patients with del(17p) had the worse outcomes with a median PFS of 7 months and median survival of 16 months.[125] The most common grade 3 or 4 adverse events included hematologic toxicities (50% of patients) and infections (13%; all grade 3 events).[125] An ongoing phase III randomized trial is evaluating outcomes with BR compared with R-chlorambucil as first-line or second-line therapy in patients with CLL who are not suitable for fludarabine-based chemoimmunotherapy (due to older age or comorbid conditions). In an interim analysis of this trial, data from 126 patients (median age 74 years, range 44–91) were available for evaluation (BR, n = 58; R-chlorambucil, n = 68).[126] Among patients who received second-line therapy (n = 51; relapse occurred >12 months since last dose of first-line treatment), the ORR was 89% in the BR group (CR in 11%) and 83% (CR in 4%) in the R-chlorambucil group.[126]

The results of recent phase III trials have showed that the addition of idelalisib or ibrutinib to BR significantly improves PFS in patients with relapsed or refractory CLL.[127,128] 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 21 months, the median OS was not reached for BR plus idelalisib versus 41 months for BR plus placebo (P = .036).[127] The improvement in OS was observed across risk groups; however, the incidence of opportunistic infections and severe adverse events were more frequent in the idelalisib arm. 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. 13.3 months; $P < .0001$).[128] The PFS at 18 months (as assessed by the independent review committee) was 79% and 24%, respectively.

HDMP in combination with rituximab was shown to be well tolerated and an active therapy for patients with refractory CLL, including in those with unfavorable prognostic features. In several small studies, treatment with HDMP combined with rituximab resulted in ORR of 78% to 93% with CR in 14% to 36% of patients; median PFS (or time to progression) was 7 to 15 months, and one study reported a median survival of 20 months.[129-131] In addition, this regimen was shown to be active in patients with fludarabine-refractory disease and/or del(17p).[129,130] 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.[129,131]

Initial phase II studies of lenalidomide monotherapy for patients with relapsed or refractory CLL showed ORRs of 32% to 47% and CR rates of 7% to 9%.[132,133] Among the subgroup of patients with del(11q), the ORR was 39% to 47%; the ORR in the small subgroup of patients with del(17p) was only 13%.[132,133] Myelosuppression and tumor flare reactions were the most common grade 3 or 4 adverse events. 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.[134] 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).[135,136]At a median follow-up time of 24 months, the ORR, median PFS, and median OS were 40.4%, 9.7 months, and 33.0 months, respectively.[136] PFS and OS were significantly different between responders and patients with stable disease (median PFS: 26.5 vs. 7.2 months, $P < .001$; median OS: not reached vs. 19.8 months; $P = .011$). Lenalidomide also showed modest activity in patients with unfavorable cytogenetic profiles, with ORR of 36.1%, 39.1%, and 21.7%, respectively, in patients with TP53 mutations, unmutated *IGHV*, and del(17p).[136]

Lenalidomide (initial dose 10 mg daily started on day 9 of cycle 1; given 28 days of a 28-day cycle) in combination with rituximab (375 mg/m^2 weekly for 4 weeks in cycle 1, then on day 1 of cycles 3–12) was evaluated in a phase II study of patients with relapsed or refractory CLL (N = 59; median 2 prior regimens).[137] The ORR was 66% with CR in 12%; all CRs were observed after 12 or more cycles of therapy. The median time to treatment failure was 17 months for all patients. The median OS was reached, with an estimated 3-year OS rate of 71%. Among the subgroup of patients with del(17p) (n = 15), the ORR was 53%, which was not significantly different from the 70% ORR among patients without del(17p). However, the subgroup of patients considered fludarabine refractory (n = 12) had decreased ORR compared with those who were sensitive (33% vs. 70%; $P = .04$). In addition, patients with del(17p) who were also fludarabine refractory had the worse survival outcomes, with a median OS of less than 10 months. The most common grade 3 or 4 toxicity included neutropenia (74%), thrombocytopenia (34%), and infections or febrile episodes (24%). Tumor flare reactions occurred in 27% of patients, but all were grade 1 or 2 events.[137]

Ofatumumab has demonstrated activity in patients with CLL refractory to fludarabine and alemtuzumab or in patients for whom alemtuzumab

is contraindicated due to bulky lymphadenopathy.[138] 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 [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.[138] The median PFS was 4.6 months and 5.5 months, respectively, for patients with FA-ref CLL and BF-ref CLL. The median OS was 14 months and 17.4 months for the FA-ref and the BF-ref groups, respectively. The most common ≥grade 3 adverse events were infections (24%) and neutropenia (12%). Ofatumumab is approved for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. 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.[139] 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 20.2 months, respectively. The COMPLEMENT 2 study evaluated the combination of FC plus ofatumumab versus FC alone in patients with relapsed CLL (n = 365).[140] FC plus ofatumumab was associated with improved PFS with manageable safety profile. The median PFS (primary endpoint; assessed by the independent review committee) was 28.9 months and 18.8 months, respectively, for the combination of FC plus ofatumumab and FC (*P* = .0032). 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.

Obinutuzumab has monotherapy activity in patients with heavily pretreated relapsed or refractory CLL. In a phase II study (GAUGIN 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.[141] A subset analysis of the CLL11 study showed that the combination of obinutuzumab plus chlorambucil was also active in patients with CLL refractory to prior treatment with chlorambucil.[142] Among the 30 patients who crossed over to obinutuzumab plus chlorambucil, clinical response was seen in 87% of patients (77% PR, 7% CR, and 3% incomplete CR). The median PFS from start of crossover treatment was 17.2 months.

Alemtuzumab, either as monotherapy or in combination with rituximab has demonstrated activity in patients with fludarabine-refractory del (17p) CLL or CLL with *TP53* abnormalities.[143-145] In a phase II study, alemtuzumab induced significant responses in patients with fludarabine-refractory CLL (n = 93), with an ORR of 33% (CR, 2%).[143] The median time to progression was 4.7 months for all patients (9.5 months for responders) and the median OS was 16 months (32 months for responders).[143] In a retrospective analysis that included 202 patients with pretreated CLL and del(17p), alemtuzumab was associated with favorable ORR (32%) and median PFS and OS (6.2 months and 21 months, respectively).[145] Myelosuppression and infections were the most common grade 3-4 toxicities. It should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.[143,145] Subcutaneous alemtuzumab was also as effective and safe as intravenous alemtuzumab in patients with advanced-stage relapsed or refractory CLL.[146-149] CMV reactivation can occur in about 10% to 25% of patients

treated with alemtuzumab.[143,145-147,150] Appropriate anti-infective prophylaxis and routine monitoring for early signs of infectious complications and CMV reactivation are warranted when administering alemtuzumab-containing regimens.

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.[151] 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 versus 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.

Lenalidomide maintenance following second-line therapy was evaluated in a phase III randomized multicenter trial (CONTINUUM Trial).[152] 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 (33.9 months vs 9.2 months). Neutropenia (66.2% vs 30.5%) and diarrhea (40.8% vs 16.2%) were the most common adverse events in the lenalidomide and placebo arms respectively. The incidences of febrile neutropenia (1.9% vs 0%) deep vein thrombosis (1.9% vs 0%) and pulmonary embolism (2.5% vs 0.6%) were higher in the lenalidomide arm compared to placebo.

Allogeneic Hematopoietic Stem Cell Transplant

Retrospective studies showed that allogeneic hematopoietic cell transplant (HCT) can overcome the poor prognosis associated with del(17p) and can result in long-term PFS.[153-158] In a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT), allogeneic HCT induced long-term remission in patients with del(17p).[154] At a median follow-up period of 39 months, 3-year PFS and OS rates were 37% and 44%, respectively. 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 (defined as refractoriness to fludarabine-based therapy or the presence of unfavorable cytogenetic abnormalities), independent of the presence of *TP53*, *SF3B1*, and *NOTCH1* mutations.[156] 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.[156] 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).[158]

It is understood that studies involving allogeneic HCT are subject to significant selection biases. Nonetheless, available evidence from non-randomized studies suggest that allogeneic HCT may be 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).[159] At the present time, given the extremely favorable outcome of patients with del(17p) treated with ibrutinib as first-line therapy[102,104] and the availability of venetoclax as an effective treatment option for relapsed or refractory CLL with del (17p),[115,116] allogeneic HCT is not considered as a reasonable treatment option for patients in remission after first-line therapy even for patients with del(17p) or *TP53* mutation.

Treatment Recommendations

Assessment of Functional Status and Comorbidity

CLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. Approximately 70% of patients are diagnosed at age ≥65 years and 40% of patients are diagnosed at age ≥75 years.[160] Comorbidities are frequently present in older patients. In addition, organ function and bone marrow reserve also decline with advancing age. The tolerability of a treatment regimen relative to a patient's physical fitness is an important consideration in the management of CLL. 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 CrCl was used by the GCLLSG to assess the overall fitness of patients enrolled in clinical trials.[161,162] 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 vascular system and 12% of patients had cardiac comorbidities.[162] The presence of multiple comorbidities (≥2 comorbidities) was an independent predictor of clinical outcome independent of patients' age or disease stage.[162] The median OS (71.7 vs. 90.2 months; $P < .001$) and PFS (21.0 vs. 31.5 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. Older patients with adequate functional status can be treated with more active or intensive therapies,[163] and should be evaluated for cytogenetic abnormalities by FISH. Patient age and the presence or absence of del(17p) or *TP53* mutation should then help to direct treatment options, as shown below.

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. 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) may benefit from treatment if they become symptomatic or show evidence of progressive disease.[3] A "watch and wait" approach is often appropriate in the absence of disease symptoms. 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.

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] Indications for initiating treatment include severe fatigue, weight loss, night sweats, and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); progressive anemia or thrombocytopenia; or autoimmune anemia/thrombocytopenia unresponsive to corticosteroids.[3] Asymptomatic patients should be observed until such indications (as mentioned above) become apparent. Recommendations for patients with indications for treatment are based on patient's age or functional status (comorbidity index/performance status) as well as the presence or absence of del(17p) or *TP53* mutation.

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.[164] 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.[165] Based on these data, the panel decided to change the age cutoff from 70 years to 65 years.

CLL Without del(17p) or TP53 Mutation

First-line Therapy

Obinutuzumab plus chlorambucil (category 1),[95,96] ibrutinib (category 1),[105] and ofatumumab plus chlorambucil[98] are the preferred treatment options for frail patients with significant comorbidity (not able to tolerate purine analogs) or patients ≥65 years and younger patients with significant comorbidities). In the CLL11 trial, there was a clinically meaningful improvement in PFS with a trend towards improved OS in patients treated with obinutuzumab + chlorambucil versus rituximab + chlorambucil.[95,96] Therefore, rituximab plus chlorambucil should be reserved for patients who cannot tolerate obinutuzumab. Bendamustine with or without rituximab is a reasonable alternative for patients ≥65 years that are otherwise eligible for chemoimmunotherapy.[83,85]

With multiple randomized studies showing a survival advantage for combination regimens containing chlorambucil or rituximab compared to monotherapy with either of these agents,[95,98] 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.[166,167] Obinutuzumab (category 2B),[97] rituximab (category 3),[166] or chlorambucil (category 3)[167] are included as alternate treatment options.

In patients <65 years without significant comorbidities, fludarabine-based chemoimmunotherapy has emerged as the

standard of care, especially in those with mutated *IGHV*.[39,79] Data from the final analysis of the CLL10 study confirmed the superiority of FCR over bendamustine plus rituximab in patients ≤65 years, without significant comorbidities.[85] Chemoimmunotherapy with FCR is the preferred treatment option (category 1) for patients <65 years without significant comorbidities. FR, PCR, or bendamustine with or without rituximab are included as alternate options for chemoimmunotherapy. An oral formulation of fludarabine was investigated and is approved by the FDA for the treatment of patients with CLL (who have not responded to or progressed after treatment with at least one alkylating agent).[168-170] 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.

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 trial (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).[105] However, with the recent FDA approval, some panel members agreed that ibrutinib may be an appropriate option instead of chemoimmunotherapy in younger patients with unmutated IGHV who do want to enroll in a clinical trial. Therefore, based on the recent FDA approval, the panel included ibrutinib with a category 2A recommendation for first-line therapy for patients <65 years without del(17p).

Lenalidomide maintenance after first-line therapy is recommended for high-risk patients (MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated *IGHV*).[107]

Relapsed or Refractory Therapy

Ibrutinib (category 1),[108,109] idelalisib + rituximab (category 1),[111] idelalisib,[113] and venetoclax ± rituximab (particularly for patients deemed intolerant or refractory to ibrutinib or idelalisib)[116,118] are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities. Bendamustine + rituximab, with idelalisib or ibrutinib are also included as alternate options for chemoimmunotherapy regardless of the patients' age and comorbidities.[127,128]

For frail patients with significant comorbidity or patients ≥65 years and younger patients with comorbidities, reduced-dose FCR or PCR, bendamustine with or without rituximab, HDMP or chlorambucil with rituximab, monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or dose-dense rituximab are included as alternative options. For patients <65 years without significant comorbidities, chemoimmunotherapy (FCR, FC + ofatumumab, PCR, bendamustine with or without rituximab, CHOP with rituximab, OFAR), monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or HDMP with rituximab are included as alternative options.

Lenalidomide maintenance or ofatumumab maintenance (category 2B) is recommended for patients who are in complete or PR to second-line therapy.[151,152] Allogeneic HCT can be considered for select patients (without significant comorbidities) after reinduction of remission.

CLL with del(17p) or TP53 Mutation

Outcomes remain poor with currently available chemoimmunotherapy regimens. Enrollment in an appropriate clinical trial is recommended for patients with del(17p). In the absence of appropriate clinical trials in the patient's local area, ibrutinib is the preferred treatment option for first-line therapy.[102,104] HDMP plus rituximab,[129,130] obinutuzumab + chlorambucil,[95] and alemtuzumab with or without rituximab[143-145] are included as alternate treatment options. Fludarabine-based chemoimmunotherapy is no longer recommended as an option for first-line chemoimmunotherapy for del(17p) CLL.[120]

The efficacy of ibrutinib in patients with del(17p) patients exceeds the results of alternative regimens in the upfront and salvage settings and should be considered as the best choice in the absence of a contraindication to give this treatment. Recent reports suggest that complex karyotype (≥3 unrelated chromosomal abnormalities in more than one cell on CpG-stimulated karyotype of CLL cells) is a stronger predictor of poor clinical outcomes than del(17p) in patients with relapsed or refractory CLL treated with ibrutinib-based regimens.[171,172] In an analysis of 88 patients with relapsed or refractory CLL treated with ibrutinib-based regimens, in a multivariate analysis, only the complex karyotype was significantly associated with inferior EFS ($P = .006$), whereas fludarabine-refractory CLL ($P = .005$) and complex karyotype ($P = .008$) were independently associated with inferior OS.[172] Complex karyotype has also been identified as an independent prognostic factor for shorter time-to-first-treatment.[173] CpG-stimulated karyotyping is useful to identify high-risk patients, particularly for treatment with ibrutinib.

Patients with response to first-line therapy should be considered for allogeneic HCT, 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 SCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics.[174] Allogeneic HCT is not recommended for patients with del (17p) responding to first-line therapy with ibrutinib, if complex karyotype is not present. Lenalidomide maintenance after first-line therapy is recommended for high-risk patients (MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated *IGHV*).[107]

Patients with no response to first-line therapy should be enrolled in clinical trials or be treated with second-line therapy for relapsed or refractory disease. Ibrutinib,[108-110] venetoclax ± rituximab,[115,118] idelalisib + rituximab,[112] and idelalisib[113] are the preferred options for relapsed or refractory disease. Lenalidomide maintenance or ofatumumab maintenance (category 2B) is recommended for patients who are in CR or PR to second-line therapy.[151,152]

Histologic Transformation

About 2% to 10% of patients with CLL will develop Richter's transformation (histologic transformation to DLBCL or Hodgkin lymphoma) during the course of their disease and treatment.[175-177] The incidence of histologic transformation increases with the number of prior regimens. Inactivation of NOTCH1 and disruption of TP53 and CDKN2A/B have been identified as possible genetic pathways involved in the pathogenesis of Richter's transformation.[178,179]

Richter's transformation should be treated with chemoimmunotherapy regimens initially developed for DLBCL.[180,181] OFAR and hyper-CVAD with rituximab were also used for the treatment of patients with Richter's transformation.[123,124,182] Allogeneic HCT can also be considered following a response to initial therapy in patients with Richter's transformation.[180] 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 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).[180] HDT/ASCR 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, co-morbidities, or lack of a suitable donor.[183]

Patients with histologic transformation to Hodgkin lymphoma should receive a standard regimen used for the treatment of Hodgkin lymphoma. Other histologic transformations such as CLL with increased prolymphocytes (CLL-PL) or accelerated CLL (presence of expanded proliferation centers or a high proliferation rate) are associated with a more aggressive disease course and optimal management was not established.

Special Considerations for the Use of Small Molecule Inhibitors (Ibrutinib and Idelalisib)

Ibrutinib 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.[62,63] This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and may persist for several weeks on treatment. 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.[62]

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.[102,105] The benefit and risk of ibrutinib should be evaluated in patients requiring anti-platelet or anticoagulant therapies. Patients requiring warfarin have been excluded from clinical trials evaluating ibrutinib. Ibrutinib should not be given concomitantly with warfarin. 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.[102] Switching to alternate therapy should be considered especially in patients with hypertension that is not medically controllable. 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. Recent reports suggest that resistance to ibrutinib is primarily mediated through mutations in *BTK* and *PLCG2* genes.[184,185] In a single institution cohort study, among 46 patients with progressive CLL on ibrutinib, 39 patients (84.8%) had mutations in *BTK* and/or *PLCG2*.[185] These findings suggest that testing for these mutations may be helpful to predict clinical relapse in patients receiving ibrutinib.

Fatal and/or serious hepatotoxicity (transaminase elevations), severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.[186] Hepatotoxicity is a major concern in younger patients treated with idelalisib as first-line therapy.[187] Close monitoring of transaminase levels is essential and concurrent administration of idelalisib with other hepatotoxic drugs should be avoided. Idelalisib is also associated with opportunistic infections and febrile neutropenia. Pneumocystis jirovecii pneumonia (PJP) and CMV reactivation have been reported in patients treated with idelalisib, and the risk of developing these opportunistic infections is highest in the first 6 months of treatment.[127] The addition of CD20 monoclonal antibody or

chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia. Appropriate anti-infective prophylaxis and routine monitoring for early signs of infectious complications and CMV reactivation (as described below) is recommended for patients receiving idelalisib.

Supportive Care

Infections

Patients with CLL are susceptible to infectious complications due to the underlying disease as well as treatment with immunosuppressive chemotherapy agents. Infectious complications are influenced by the progressive reduction in immunoglobulin levels and are more common in previously treated patients.[188] Hypoglobulinemia was shown to be present in about 40% of patients up to 3 years prior to diagnosis of CLL.[189] Heavily pretreated patients who become refractory to fludarabine have high susceptibility to developing serious infections. In a retrospective analysis, 89% of patients with fludarabine-refractory CLL developed infectious complications requiring hospitalization.[190] In randomized studies, intravenous immunoglobulin (IVIG) was associated with a significant decrease in the occurrence of infections but with no improvement in OS outcome.[191-195] Protein and conjugate vaccines were shown to induce better responses than plain polysaccharide vaccines.[196,197] Administration of IVIG (for recurrent infections and if IgG levels <500 mg/dL), antiinfective prophylaxis, and vaccinations are the main options available to minimize the possibilities of developing infectious complications.

In selected patients (serum IVIG <500 mg/dL) with recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization, the NCCN Guidelines recommend monitoring IVIG levels and administering monthly IVIG (0.3–0.5 g/kg) to maintain nadir levels of approximately 500 mg/dL. The use of antiinfective prophylaxis is also appropriate for the management of patients who may be susceptible to certain infections due to a given treatment regimen. Antiviral and pneumocystis prophylaxis is recommended for patients receiving purine-analog, idelalisib, corticosteroids, and/or alemtuzumab during treatment and thereafter. Acyclovir or equivalent is recommended for herpes virus and sulfamethoxazole trimethoprim or equivalent is recommended for *Pneumocystis* pneumonia (PCP) prophylaxis. Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients.[198] 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.

Hepatitis B virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents.[199,200] HBV carriers have high risk of HBV reactivation. Fulminant hepatitis, hepatic failure and death associated with HBV reactivation have occurred in patients receiving CD20 mAb containing regimens, including rituximab, obinutuzumab or ofatumumab.[201] HBV reactivation has also been reported in patients treated with alemtuzumab and idelalisib. Recommend HBV prophylaxis and monitoring is recommended in high-risk patients receiving CD20 mAbs (rituximab, obinutuzumab or ofatumumab), alemtuzumab, purine analogs, and idelalisib.

HBsAg and HBcAb testing is recommended for all patients receiving CD20 mAb therapy. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative polymerase chain reaction (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 intravenous immunoglobulin (IVIG) may be HBcAb positive as

a consequence of IVIG therapy, although HBV viral load monitoring is recommended.[202]

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.[203,204] 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 mAb 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.[205]

Cytomegalovirus Reactivation

CMV reactivation is well-documented in patients receiving treatment with alemtuzumab, occurring in up to 25% of patients.[206] Clinicians should be aware of the high risk of CMV reactivation in patients with CLL treated with idelalisib or alemtuzumab. Monitoring for the presence of CMV antigens regularly using quantitative PCR assays is an effective approach to the management of CMV reactivation.[207] Current practices for the management of CMV reactivation include the use of prophylactic ganciclovir if CMV viremia is present prior to alemtuzumab therapy,[206] or preemptive use of these drugs when the viral load is found to be increasing during therapy.[208,209] The NCCN Guidelines recommend routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with idelalisib or alemtuzumab and for 2 months following completion of treatment. 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.[210,211] Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias.

AIHA is the most common form of autoimmune cytopenia. 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.[212] 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.[212-215] 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.[212,216] 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.[217] 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.[217]

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine,[218] and splenectomy should be used in steroid-refractory

cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias.[219-225] Synthetic thrombopoietin-like agents such as romiplostim and eltrombopag have shown promising results in the treatment of thrombocytopenia associated with ITP.[226-229] 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.[211] 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.[211]

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)[90,91] and in approximately 30% to 60% of patients with relapsed or refractory CLL.[132,133] Tumor flare was more frequent among patients with enlarged (>5 cm) lymph nodes at baseline.[133] 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 was associated with increased risks for venous thromboembolism (VTE) in patients with myelodysplastic syndromes or multiple myeloma, particularly when combined with dexamethasone or with chemotherapy agents.[92,230-234] Lenalidomide may also be associated with VTE in patients with CLL/SLL[132,133,235] 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 these recommendations may differ from the NCCN Guidelines for Venous Thromboembolic Disease in which the recommendations for VTE associated with lenalidomide pertain only to patients with multiple myeloma.

Tumor Lysis Syndrome

Patients with CLL and high WBC counts may occasionally experience TLS and should be managed as outlined under *Tumor Lysis Syndrome* in the *Supportive Care* section of the algorithm.

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

progression free, 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 which 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) and venetoclax ± rituximab are effective treatment options for relapsed/refractory del(17p) CLL/SLL. Careful monitoring of adverse events after initiation of treatment and supportive care for the treatment-related complications should be an integral part of management of CLL/SLL.

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