National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

NCCN Evidence Blocks™

Version 2.2020 — October 8, 2019

NCCN.org

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NCCN Guidelines Version 2.2020
Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma
NCCN Evidence Blocks™

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Þ Internal medicine
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To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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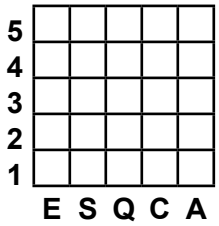
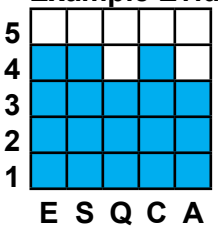
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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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 fluorescence in situ hybridization (FISH) for t(11;14); t(11q;v). CD200 may be useful to distinguish from mantle cell lymphoma (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 (ie, immunohistochemistry [IHC], flow cytometry) may be sufficient for diagnosis.
  - Adequate immunophenotyping to establish diagnosis by IHC:[b] CD3, CD5, CD10, CD20, CD23, cyclin D1. LEF1 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]

CLL/SLL → See Workup (CSLL-2)

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

→ Observe

[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 (ie, CD23 dim or negative, CD20 bright, sIg bright).

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

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

[e] 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: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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.

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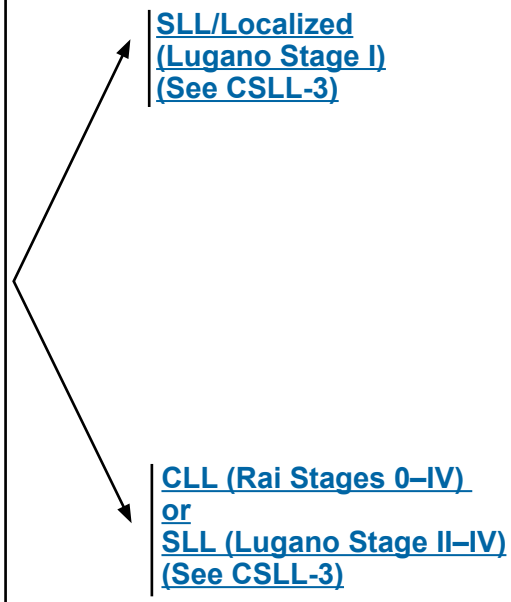
WORKUP

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
- Lactate dehydrogenase (LDH)
- Uric acid
- Unilateral bone marrow aspirate + biopsy[g]
- Hepatitis B[h] or C testing if treatment contemplated
- Multigated aquisition (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. CT scans may be warranted for the evaluation of symptoms of bulky disease or for the assessment of risk for TLS prior to initiating venetoclax.
[g] May be informative for the diagnosis of immune-mediated or disease-related cytopenias.
[h] Hepatitis B testing is indicated because of the risk of reactivation during treatment (eg, immunotherapy, chemoimmunotherapy, chemotherapy, targeted therapy). See Treatment and Viral Reactivation (CSLL-C 1 of 4). Tests include hepatitis B surface antigen (HBsAg) and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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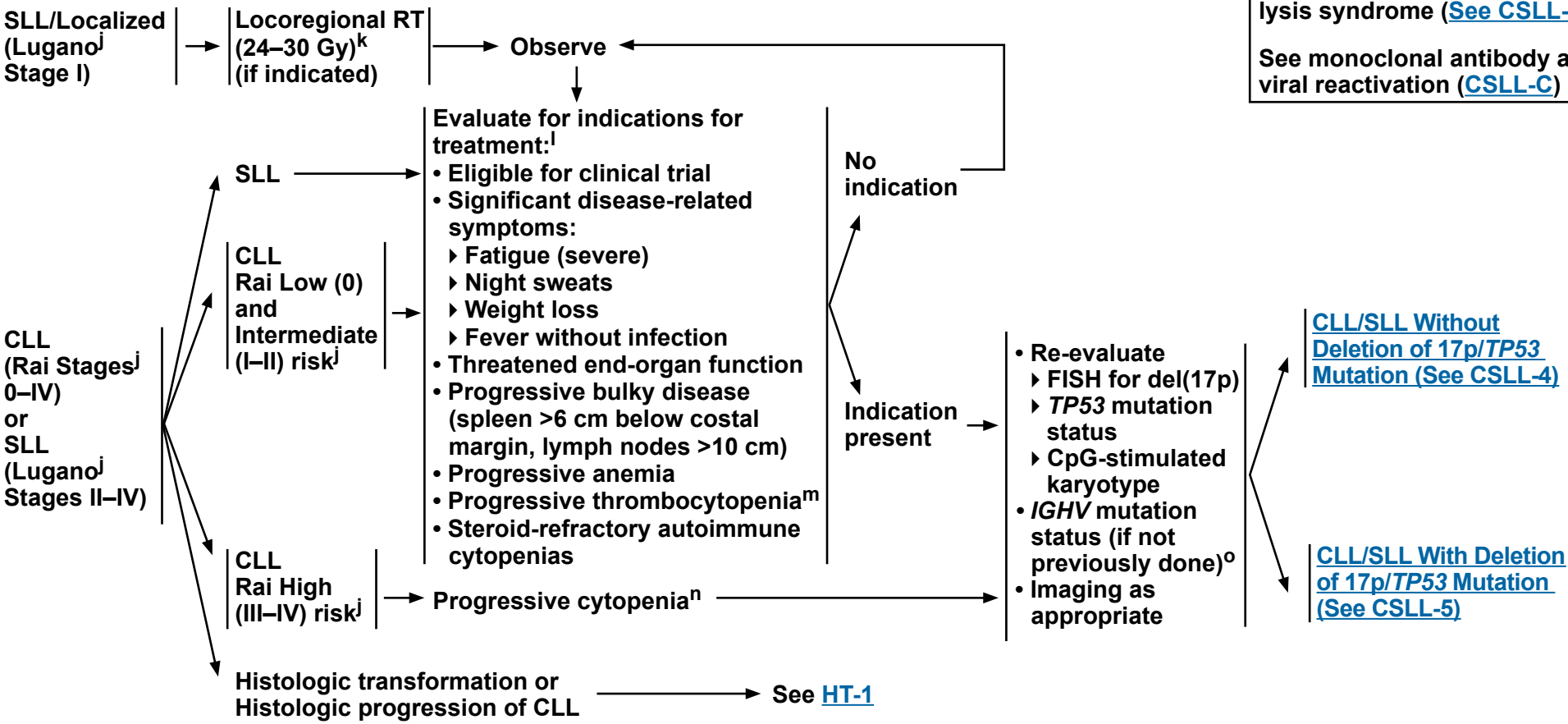
PRESENTATION[i]

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

See monoclonal antibody and viral reactivation (CSLL-C)



[i] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[j] See Rai and Binet Classification Systems (CSLL-B 1 of 2) and Lugano Modification of Ann Arbor Staging System (CSLL-B 2 of 2).
[k] The dose is delivered in 1.5–2.0 Gy/fraction. See NCCN Guidelines for B-Cell Lymphomas, Principles of Radiation Therapy for additional details.
[l] Absolute lymphocyte count alone or symptoms related to leukostasis are not an indication for treatment. Leukostasis is rarely seen in patients with CLL.
[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-evaluate when considering treatment with chemoimmunotherapy.

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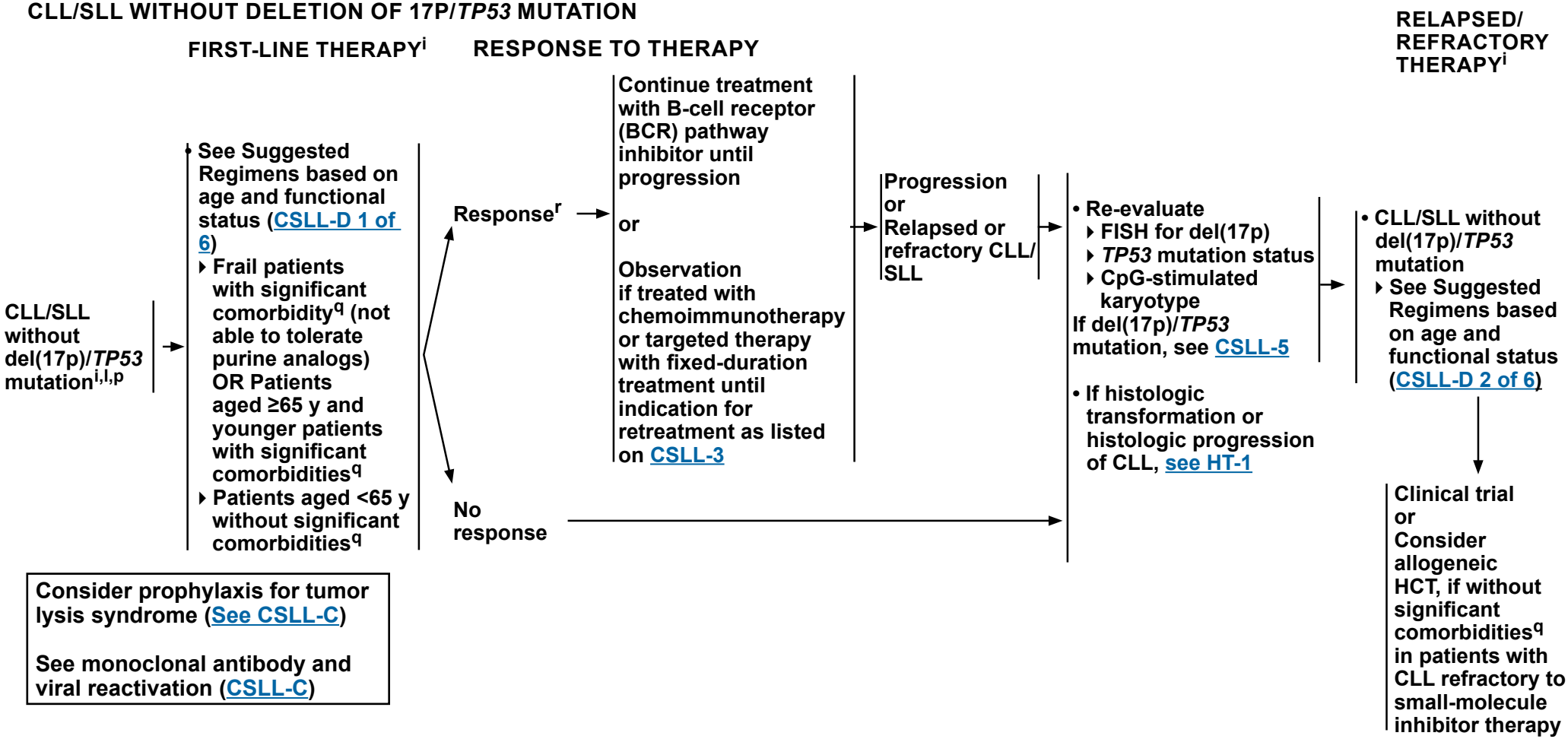
CLL/SLL WITHOUT DELETION OF 17P/*TP53* MUTATION



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

See monoclonal antibody and viral reactivation (CSLL-C)

[i] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[l] Absolute lymphocyte count alone or symptoms related to leukostasis are not an indication for treatment. Leukostasis is rarely seen in patients with CLL.
[p] Given incurability with conventional therapy, consider including clinical trial as first-line therapy.
[q] ElSawy M, Storer BE, Pulsipher MA, et al. Multi-centre validation of the prognostic value of the haematopoietic cell transplantation-specific comorbidity index among recipient of allogeneic haematopoietic cell transplantation. Br J Haematol 2015;170:574-583.
[r] See Response Definition after Treatment for CLL/SLL (CSLL-E).

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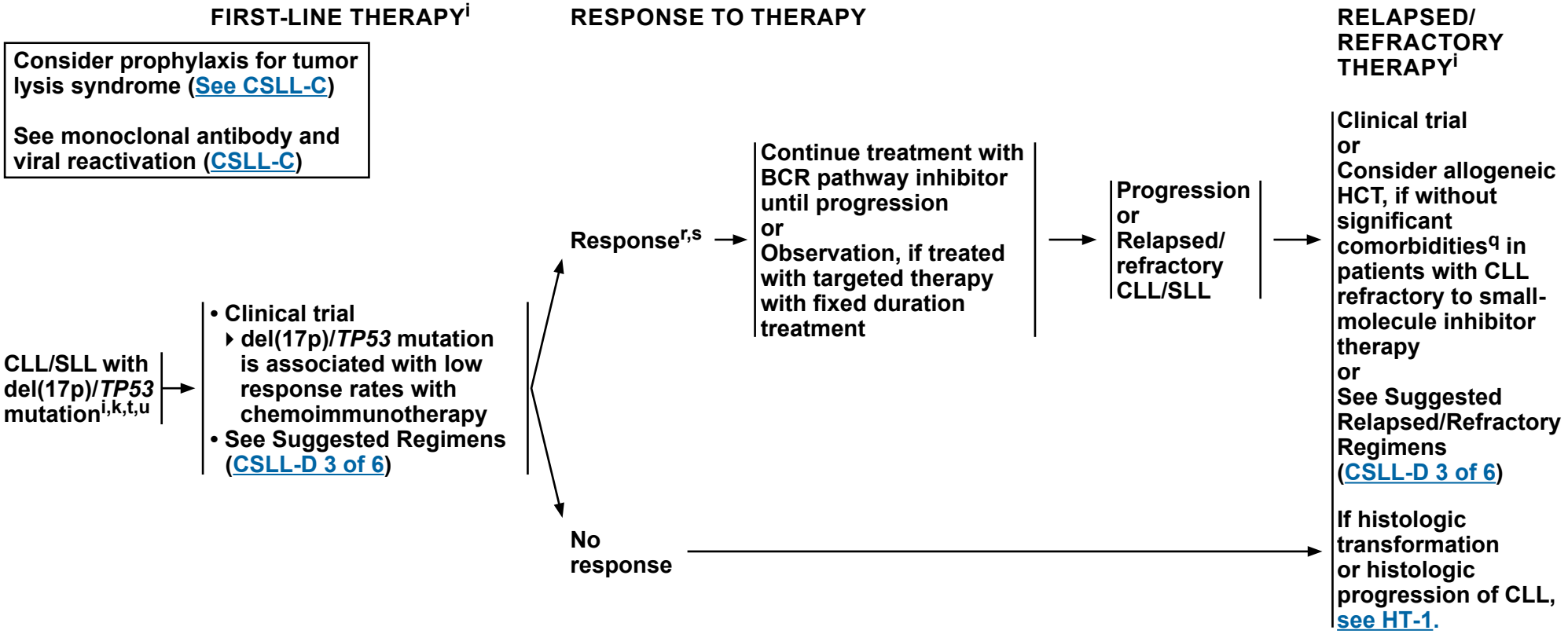
CLL/SLL WITH DELETION OF 17P/*TP53* MUTATION



[i] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[k] Absolute lymphocyte count alone or symptoms related to leukostasis are not an indication for treatment. Leukostasis is rarely seen in patients with CLL.
[q] ElSawy M, Storer BE, Pulsipher MA, et al. Multi-centre validation of the prognostic value of the haematopoietic cell transplantation-specific comorbidity index among recipient of allogeneic haematopoietic cell transplantation. Br J Haematol 2015;170,574-583.
[r] See Response Definition after Treatment for CLL/SLL (CSLL-E).
[s] For patients with complex karyotype (≥3 abnormalities) achieving remission with or after BTK inhibitor therapy, consider discussion of allogeneic HCT; however, available data do not support this as highly effective (Jaglowski et al. Br J Haematol 2012;159:82-87).
[t] CPG-stimulated karyotype is useful to identify high-risk patients, particularly for Bruton's tyrosine kinase (BTK) inhibitor therapy.
[u] Patients with low percentage of del17p-positive cells should be retested due to chance of false-positive results.

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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%**
Zap70	**<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 for survival and time to progression in patients who received treatment.
[b] *IGHV* rearrangements involving VH3-21 carry a poor prognosis even if mutated. *TP53* mutation status also provides additional prognostic information to FISH.
[c] *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. The presence of del(11q) and/or del(17p) are associated with short progression-free survival (PFS) with chemotherapy and chemoimmunotherapy approaches.
[e] Complex karyotype is based on results of conventional karyotyping of stimulated CLL cells.

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CLL STAGING SYSTEMS

Rai System[a]

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

Binet System[b]

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

[a] This research was originally published in Blood. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. (c) The American Society of Hematology.
[b] From: Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.
[c] Immune-mediated cytopenias are not the basis for these stage definitions.

Continued

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SLL STAGING SYSTEM

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

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

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

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Anti-infective Prophylaxis

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

Treatment and Viral Reactivation

Hepatitis B virus (HBV):

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

Treatment and Viral Reactivation *(continued)*

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

Hepatitis C virus (HCV):

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

CMV reactivation:

- Clinicians must be aware of the high risk of cytomegalovirus (CMV) reactivation in patients receiving fludarabine-based chemoimmunotherapy, idelalisib, or alemtuzumab. The current recommendations for appropriate screening are controversial. CMV viremia should be measured by polymerase chain reaction (PCR) quantitation at least every 2–3 weeks. Some clinicians use ganciclovir (oral or IV) pre-emptively if viremia is present; others use ganciclovir only if viral load is rising. Consultation with an infectious disease expert may be necessary.

John Cunningham (JC) virus:

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

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Tumor Lysis Syndrome (TLS)

- **Laboratory hallmarks of TLS:**
  - **High potassium**
  - **High uric acid**
  - **High phosphorous**
  - **Low calcium**
  - **High LDH**

- **Symptoms of TLS:**
  - **Nausea and vomiting, shortness of breath, irregular heartbeat, clouding of urine, lethargy, and/or joint discomfort.**

- **TLS features**
  - **Consider TLS prophylaxis for patients with the following risk factors:**
    - ◊ **Patients receiving treatment with venetoclax (See CSLL-G), chemoimmunotherapy, lenalidomide, and obinutuzumab**
    - ◊ **Progressive disease after small-molecule inhibitor therapy**
    - ◊ **Bulky lymph nodes**
    - ◊ **Spontaneous TLS**
    - ◊ **Elevated white blood cell (WBC) count**
    - ◊ **Pre-existing elevated uric acid**
    - ◊ **Renal disease or renal involvement by tumor**

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

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

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

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

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

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

Non-Melanomatous Skin Cancer
- Patients with CLL/SLL have a higher risk of developing non-melanomatous skin cancers.
- Risk factors include caucasians and a history of intensive sun exposure at a young age.
- Annual dermatalogic skin screening is recommended.

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

Rituximab Rapid Infusion and Subcutaneous Administration
- If no severe infusion reactions were experienced with prior cycle of rituximab, a rapid infusion over 90 minutes can be used.
- Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route.

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

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Thromboprophylaxis

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

Tumor Flare Reactions

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

Use of Small-Molecule Inhibitors

- See Special Considerations for the Use of Small-Molecule Inhibitors (CSLL-F)

Vaccination

- Avoid all live vaccines
- Annual influenza vaccine[b] (live attenuated influenza vaccine should be avoided)
- Pneumococcal 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,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

FIRST-LINE THERAPY[e]		
Frail patient with significant comorbidity (not able to tolerate purine analogs) OR Patients aged ≥65 y and younger patients with significant comorbidities (creatinine clearance [CrCl] <70 mL/ min)	Preferred regimens • Ibrutinib[f] (category 1) • Venetoclax[f,g] + obinutuzumab	Other recommended regimens • Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) + anti-CD20 monoclonal antibody[d,h] (Not recommended for frail patients) • Chlorambucil + obinutuzumab • High-dose methylprednisolone (HDMP) + rituximab (category 2B) • Ibrutinib[f] + obinutuzumab (category 2B) • Obinutuzumab (category 2B) • Chlorambucil (category 3) • Rituximab (category 3)
Patients aged <65 y without significant comorbidities	Preferred regimens • Ibrutinib[f] (category 1) • Venetoclax[f,g] + obinutuzumab	Other recommended regimens • Bendamustine + anti-CD20 monoclonal antibody[d,h,i] • FCR (fludarabine,[j] cyclophosphamide, rituximab)[i,k] (preferred for patients with *IGHV*-mutated CLL) • FR (fludarabine,[j] rituximab)[k,l] • HDMP + rituximab (category 2B) • Ibrutinib[f] + rituximab (category 2B) • PCR (pentostatin, cyclophosphamide, rituximab) (category 3)

POST FIRST-LINE CHEMOIMMIUNOTHERAPY MAINTENANCE THERAPY
Other recommended regimen
• Consider lenalidomide for high-risk patients (blood MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated *IGHV*)[m] after first-line therapy

See Evidence Blocks on CSLL-D (EB-1)

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

See Footnotes on CSLL-D 4 of 6

See Suggested Regimens for Relapsed/Refractory Therapy for CLL/SLL without del(17p)/*TP53* mutation (2 of 6)

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

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EVIDENCE BLOCKS FOR FIRST-LINE THERAPY FOR CLL/SLL WITHOUT del(17p)/*TP53* MUTATION

Frail Patient with Significant Comorbidity OR Patients Age ≥65 y and Younger Patients with Significant Comorbidities

Preferred Regimens	
Ibrutinib	
Venetoclax/obinutuzumab	
Other Recommended Regimens	
Bendamustine/obinutuzumab*	
Bendamustine/ofatumumab*	
Bendamustine/rituximab*	
Chlorambucil/obinutuzumab	
High-dose methylprednisolone (HDMP)/rituximab	
Ibrutinib/obinutuzumab	
Obinutuzumab	
Chlorambucil	
Rituximab	

Patients <65 y without Significant Comorbidities

Preferred Regimens	
Ibrutinib	
Venetoclax/obinutuzumab	
Other Recommended Regimens	
Bendamustine/obinutuzumab	
Bendamustine/ofatumumab	
Bendamustine/rituximab	
Fludarabine/cyclophosphamide/rituximab (FCR)**	
Fludarabine/rituximab (FR)***	
High-dose methylprednisolone (HDMP)/rituximab	
Ibrutinib/rituximab	
Pentostatin/cyclophosphamide/rituximab (PCR)	

Post First-line Chemoimmunotherapy Maintenance Therapy

Other Recommended Regimens	
Lenalidomide maintenance	

*Not recommended for frail patients
**Preferred for patients with *IGHV-mutated* CLL
**Not recommended for CLL with del(11q)

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

RELAPSED/REFRACTORY THERAPY[e]			
Frail patient with significant comorbidity OR Patients aged ≥65 y and younger patients with significant comorbidities (CrCl <70 mL/min)	**Preferred regimens** • Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g]+ rituximab (category 1) • Duvelisib[f] • Idelalisib[f] + rituximab[o]	**Other recommended regimens** • Alemtuzumab[p] ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR[j,k] • HDMP + rituximab • Idelalisib[f] • Lenalidomide[q] ± rituximab	• Obinutuzumab • Ofatumumab • Reduced-dose PCR • Venetoclax[f,g] • Dose-dense rituximab (category 2B) • Bendamustine, rituximab ± ibrutinib,[f] or idelalisib[f] (not recommended for frail patients) (category 2B for BR and BR + ibrutinib; category 3 for BR + idelalisib)
Patients aged <65 y without significant comorbidities	**Preferred regimens** • Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Duvelisib[f] • Idelalisib[f] + rituximab[o]	**Other recommended regimens** • Alemtuzumab[p] ± rituximab • Bendamustine + rituximab • FC[j,k] + ofatumumab • FCR[j,k] • HDMP + rituximab • Idelalisib[f] • Lenalidomide[q] ± rituximab	• Obinutuzumab • Ofatumumab • PCR • Venetoclax[f,g] • Bendamustine, rituximab + ibrutinib[f] (category 2B) • Bendamustine, rituximab + idelalisib[f] (category 2B)

POST SECOND-LINE CHEMOIMMUNOTHERAPY MAINTENANCE THERAPY (for complete or partial response after relapsed or refractory therapy)
Other recommended regimens
• Lenalidomide[m] • Ofatumumab (category 2B)

See Evidence Blocks on CSLL-D (EB-2) and CSLL-D (EB-3)

See Footnotes on CSLL-D 4 of 6

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

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

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EVIDENCE BLOCKS FOR RELAPSED/REFRACTORY THERAPY FOR CLL/SLL WITHOUT del(17p)/*TP53* MUTATION

Frail Patient with Significant Comorbidity and Patients ≥65 y or Younger Patients with Significant Comorbidities

Preferred Regimens	
Acalabrutinib	
Ibrutinib	
Venetoclax/rituximab	
Duvelisib	
Idelalisib/rituximab	

Other Recommended Regimens	
Alemtuzumab	
Alemtuzumab/rituximab	
Chlorambucil/rituximab	
Reduced-dose FCR	
High-dose methylprednisolone (HDMP)/rituximab	
Idelalisib	
Lenalidomide	
Lenalidomide/rituximab	

Other Recommended Regimens	
Obinutuzumab	
Ofatumumab	
Reduced-dose PCR	
Venetoclax	
Dose-dense rituximab	
Bendamustine/rituximab	
Bendamustine, rituximab and ibrutinib	
Bendamustine, rituximab and idelalisib	

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EVIDENCE BLOCKS FOR RELAPSED/REFRACTORY THERAPY FOR CLL/SLL WITHOUT del(17p)/*TP53* MUTATION

Patients <65 y without Significant Comorbidities

Preferred Regimens	
Acalabrutinib	
Ibrutinib	
Venetoclax/rituximab	
Duvelisib	
Idelalisib/rituximab	

Other Recommended Regimens	
Alemtuzumab/rituximab	
Alemtuzumab	
Bendamustine/rituximab	
Fludarabine, cyclophosphamide, and ofatumumab	
Fludarabine, cyclophosphamide, and rituximab (FCR)	
High-dose methylprednisolone (HDMP)/rituximab	
Idelalisib	
Lenalidomide	
Lenalidomide/rituximab	
Obinutuzumab	
Ofatumumab	
Pentostatin, cyclophosphamide, and rituximab (PCR)	
Venetoclax	
Bendamustine, rituximab and ibrutinib	
Bendamustine, rituximab and idelalisib	

Post Second-line Chemoimmunotherapy Maintenance Therapy

Other Recommended Regimens	
Lenalidomide maintenance	
Ofatumumab maintenance	

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

FIRST-LINE THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Ibrutinib[f] • Venetoclax[f,g] + obinutuzumab	• Alemtuzumab[p] ± rituximab • HDMP + rituximab • Obinutuzumab

RELAPSED/REFRACTORY THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f,n] (category 1) • Ibrutinib[f] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Duvelisib[f] • Idelalisib[f] + rituximab[o] • Venetoclax[f,g]	• Alemtuzumab[p] ± rituximab • HDMP + rituximab • Idelalisib[f] • Lenalidomide[q] ± rituximab • Ofatumumab[r]

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

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

See Evidence Blocks on CSLL-D (EB-4)

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EVIDENCE BLOCKS FOR THE TREATMENT OF CLL/SLL WITH del(17p)/*TP53* MUTATION

First-line Therapy

Preferred Regimens	
Ibrutinib	
Venetoclax/obinutuzumab	
Other Recommended Regimens	
Alemtuzumab	
Alemtuzumab/rituximab	
High-dose methylprednisolone (HDMP)/rituximab	
Obinutuzumab	

Relapsed/Refractory Therapy

Preferred Regimens	
Acalabrutinib	
Ibrutinib	
Venetoclax/rituximab	
Duvelisib	
Idelalisib/rituximab	
Venetoclax	
Other Recommended Regimens	
Alemtuzumab	
Alemtuzumab/rituximab	
High-dose methylprednisolone (HDMP)/rituximab	
Idelalisib	
Lenalidomide	
Lenalidomide/rituximab	
Ofatumumab	

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

[a] See references for regimens CSLL-D 5 of 6 and CSLL-D 6 of 6.
[b] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route.
[d] Re-challenge with the same monoclonal antibody is not recommended in patients experiencing rare complications (eg, mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis). It is unclear whether re-challenge with alternative anti-CD20 antibodies poses the same risk of recurrence.
[e] An FDA-approved biosimilar is an appropriate substitute for rituximab.
[f] See Special Considerations for Use of Small-Molecule Inhibitors (CSLL-F).
[g] See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[h] Anti-CD20 monoclonal antibodies include: rituximab, ofatumumab, or obinutuzumab.
[i] Data from the CLL10 study confirm the superiority of FCR over bendamustine + rituximab (BR) in younger patients. For patients >65 y, the outcome was similar for both regimens with less myelosuppression and infection for BR. FCR was associated with improved PFS (with a plateau in PFS beyond 10-year follow-up) in patients with mutated *IGHV* without del (17p)*/TP53* mutation.
[j] See Discussion for further information on oral fludarabine.
[k] 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.
[l] Not recommended for CLL with del(11q). Outcomes for CLL with del(11q) are better with chemoimmunotherapy containing an alkylating agent.
[m] Minimal residual disease (MRD) evaluation with a sensitivity of 10^{-4} according to the standardized ERIC method or standardized next-generation sequencing (NGS) method.
[n] Acalabrutinib has not been shown to be effective for ibrutinib-refractory CLL with *BTK* C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib without recurrence of symptoms.
[o] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or NCI CTCAE grade ≥3 neutropenia or grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).
[p] While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Alemtuzumab is less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.
[q] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See 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.
[r] This is not effective in patients with lymph nodes >5 cm.

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SUGGESTED TREATMENT REGIMENS
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SUGGESTED TREATMENT REGIMENS

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RESPONSE DEFINITION AFTER TREATMENT FOR CLL/SLL[a]

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

Minimal Residual Disease (MRD) Assessment:

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

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

Footnotes on CSLL-E 2 of 2

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RESPONSE DEFINITION AFTER TREATMENT FOR CLL/SLL[a,b]

[a] Hallek M, Cheson B, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.
[b] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.
[c] Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
[d] Spleen size is considered normal if <13 cm. There is no firmly established international consensus on the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.
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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS[1]

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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 continuously until progression of disease or development of side effects that require dose reduction or cessation of therapy.

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

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

Resistance
- 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.

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

Co-administration with Gastric Acid-Reducing Agents
- Avoid coadministration with proton pum inhibitors (PPIs). Stagger dosing with H2-receptor antagonists and antacids.

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

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

DUVELISIB

Dosage

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

Lymphocytosis

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

Toxicity

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

Co-administration with CYP3A Inhibitors and Inducers

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

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

Continued

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

IBRUTINIB

Dosage

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

Lymphocytosis

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

Toxicity

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

Resistance

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

Co-administration with CYP3A Inhibitors and Inducers

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

[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.

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

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

Co-administration with CYP3A Inhibitors and Inducers
- Avoid concomitant use of strong CYP3A inhibitors or inducers.
- Patients taking concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of idelalisib toxicity.

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

Continued

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

VENETOCLAX

Dosage

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

Toxicity

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

Co-administration with CYP3A Inhibitors and Inducers

- Avoid concomitant use of strong CYP3A inhibitors or inducers.

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

[2] Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. Lancet Oncol 2018;19:65-75.
[3] Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. Blood 2018;131:1704-1711.
[4] Davids M, Jones J, Eradat H, et al. Modified venetoclax dose ramp-up in select high-risk patients with chronic lymphocytic leukemia (CLL) with progression after B-cell receptor pathway inhibitors (BCRi) [abstract]. Clinical Lymphoma, Myeloma & Leukemia 2017;17:S302.
[5] Koenig K, Konstantinou D, Rogers A, et al. Rapid dose escalation of venetoclax in patients with chronic lymphocytic leukemia previously treated with B-cell receptor inhibitor therapy [abstract]. EHA Congress 2018:Abstract PF357.

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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.**
- **For patients with CrCl <80 mL/min and medium tumor burden, consider management as high risk for TLS.**

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

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

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DIAGNOSIS

ESSENTIAL:

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

→ See Workup (HT-2)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

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

[a] While occasionally an increase in proliferative rate can be shown with Ki-67, this is not considered diagnostic of a transformation.
[b] Proliferation centers in CLL may express c-MYC and/or cyclin D1. This does not change the diagnosis.
[c] First, "CLL with expanded proliferation centers" or "accelerated CLL" may be diagnosed in cases where proliferation centers in CLL are expanded or fuse together (>20x field or 0.95 mm^2) AND show Ki-67 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] IGHV sequencing of CLL and histologically transformed tissue should be done to establish the clonal relationship.

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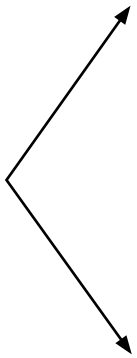
WORKUP

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

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



Richter's Transformation (HT-3)

CLL with Progression (HT-3)

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

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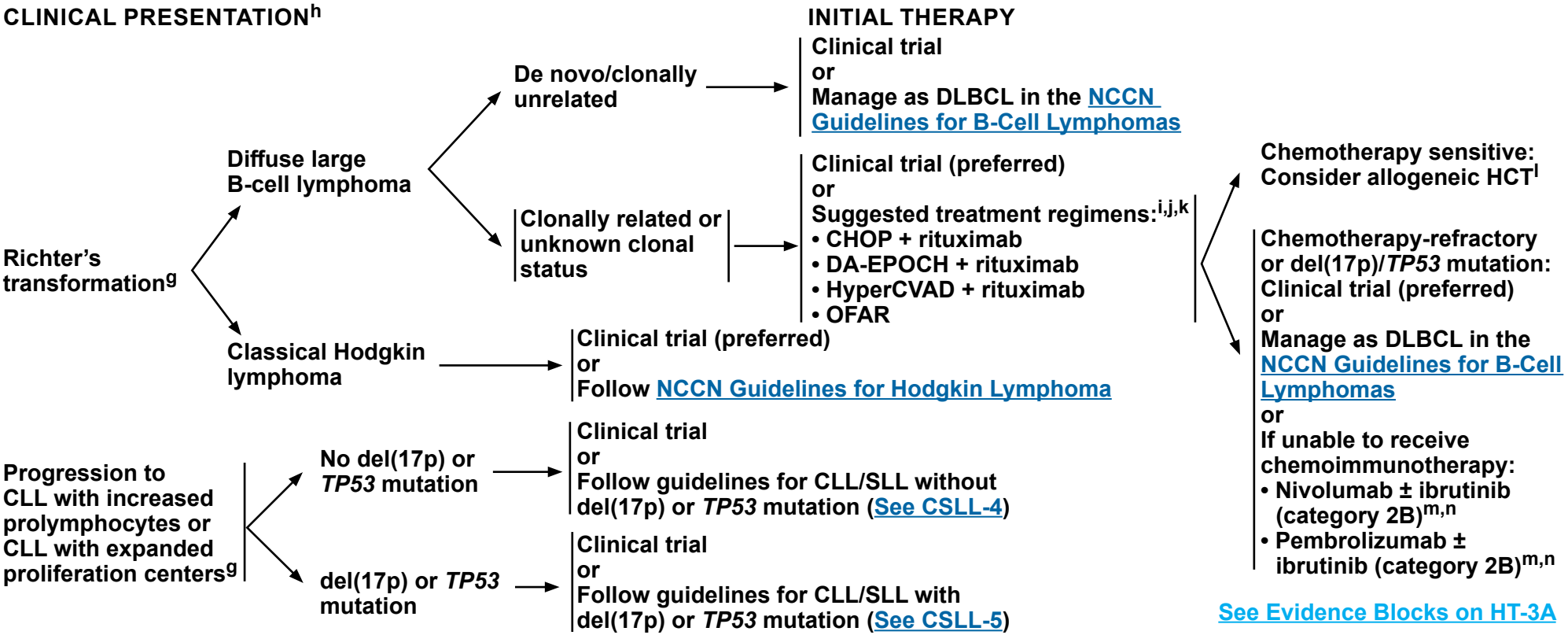

See Evidence Blocks on HT-3A

[g] "Accelerated CLL," "CLL with expanded proliferation centers," and "CLL-PLL or CLL with increased prolymphocytes" (defined on HT-1) are not considered Richter's transformation, but are associated with more aggressive disease and poorer outcome [Gine E, et al, Haematologica 2010 Sept;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).

[k] Rituximab and hyaluronidase human injection for subcutaneous use may be used in patients who have received at least one full dose of a rituximab product by intravenous route. An FDA-approved biosimilar is an appropriate substitute for rituximab.

[l] 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.

[m] See Special Considerations for Use of Small-Molecule Inhibitors (CSLL-F).

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

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EVIDENCE BLOCKS FOR THE TREATMENT OF RICHTER'S TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA
(Clonally related or unknown clonal status)

Regimens	
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)/rituximab	
Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)/rituximab	
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine)/rituximab	
OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab)	
Nivolumab	
Nivolumab/rituximab	
Pembrolizumab	
Pembrolizumab/rituximab	

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SUGGESTED TREATMENT REGIMENS REFERENCES

DA-EPOCH-R

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

HyperCVAD + rituximab

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

Tsimberidou AM, O'Brien S, 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.

Nivolumab

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

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

Pembrolizumab

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

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

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

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This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/23/2019.

Discussion

Discussion update in progress

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Overview

Chronic lymphocytic leukemia (CLL) remains the most prevalent adult leukemia in Western countries, but is considered rare in regions such as East Asia. In 2019, an estimated 20,720 people will be diagnosed with CLL in the United States, and an estimated 3,930 people will die from the disease.[1] Morphologically, the leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or prolymphocytes. CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease and are managed in much the same way.[2] CLL/SLL is characterized by a progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. The major difference is that in CLL, a significant number of the abnormal lymphocytes are found in blood in addition to bone marrow and lymphoid tissue, while in SLL there are few if any abnormal lymphocytes circulating in blood, and the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues.

Literature Search Criteria and Guidelines Update Methodology

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

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

The PubMed search resulted in 173 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update 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 at www.NCCN.org.

Staging

The Lugano Modification of Ann Arbor Staging System is used for SLL.[4] 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.[5,6] Both rely solely on physical examination (ie, presence of lymph node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden. The modified Rai classification stratifies patients into 3 risk groups.[5] 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

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and, similar to the Rai staging system, provides meaningful correlation with clinical outcome.[6]

Prognostic Factors

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

IGHV mutational status is an important predictor of survival outcomes. Unmutated *IGHV* (≥98% homology with germline gene sequence) is associated with poor prognosis and significantly decreased survival compared with mutated *IGHV*, irrespective of the stage of the disease.[7,8] In addition, *VH3-21* gene usage is associated with poor outcomes regardless of the *IGHV* mutation status (as defined by percent homology with germline sequence).[9] Unmutated *IGHV* or the *VH3-21* gene usage was shown to be an independent predictor of shorter treatment-free interval and/or survival outcomes, even when high-risk genetic abnormalities were included in the multivariable regression models.[10-13] *IGHV* mutation testing is recommended based on reproducibility and ready availability.

Cytogenetic abnormalities that can be detected by FISH are present in more than 80% of patients with previously untreated CLL. Del(13q) (55%), del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%) are the most common abnormalities.[14] 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).[14] The addition of an alkylating agent to fludarabine-based chemoimmunotherapy may help to overcome the adverse prognostic significance of del(11q) in patients with previously untreated CLL.[13,15] Del(17p), which reflects the loss of the *TP53* gene and is frequently associated with mutations in the remaining *TP53* allele, is associated with short treatment-free interval, short median survival (32 months), and poor response to chemotherapy.[14] 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.[16] 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.[17-19]

The impact of these cytogenetic abnormalities on clinical outcome has been evaluated in large prospective randomized studies.[13,20,21] In the CLL4 trial, which compared chlorambucil vs. fludarabine vs. fludarabine and cyclophosphamide (FC) as first-line therapy, *TP53* loss was found to be the strongest predictor of poor outcomes.[13] 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 progression-free survival (PFS) and overall survival (OS) outcomes.[13] In addition, del(11q) and treatment allocation were independent predictors for PFS and age was an independent predictor for OS. In the long-term follow-up from the CALGB 9712 study that

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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.[20] In the phase III randomized CLL8 study that compared FC versus FCR (fludarabine, cyclophosphamide, and rituximab) as first-line therapy, the presence of *TP53* mutation, del(17p), and unmutated *IGHV* were the strongest predictors of shorter PFS and OS.[21] The median PFS was significantly longer in patients with mutated *IGHV* treated with FCR than those treated with FC (not reached for FCR vs. 42 months for FC; $P < .001$), and the 5-year OS rates were 86% and 80%, respectively. Among patients with mutated *IGHV*, improvement in survival was seen across all cytogenetic subgroups except for those with del(17p).

The prognostic significance of del(17p) may be dependent on the proportion of malignant cells with this abnormality, and the prognosis is more favorable when the percentage of cells with del(17p) is low.[13,22] In the CLL4 trial, the presence of del(17p) in ≥10% or more cells was the strongest predictor of poor outcomes.[13] Patients with del(17p) in ≥10% cells had a response rate of 29% and a median survival of <6 months.[13] However, outcomes were similar between patient subgroups with del(17p) in 5% to 10% of cells and the subgroup with del(17p) in <5% of cells. Patients with del(17p) in 10% to 20% of cells had outcomes similar to patients with del(17p) in >20% of cells. In a more recent report that assessed the impact of cytogenetic abnormalities detected by FISH on clinical outcome in a cohort of 1585 patients with CLL, patients with del(17p) in ≤20% of cells were more likely to have mutated *IGHV*, longer median time to first treatment, and longer OS from the date of the first FISH study.[23]

Complex karyotype (≥3 unrelated chromosomal abnormalities in more than one cell on CpG-stimulated karyotype of CLL cells) is an independent predictor of significantly shorter OS and may be a stronger predictor of poor clinical outcomes than del(17p) or *TP53* mutation in patients with CLL treated with ibrutinib-based regimens.[24-29] Among patients with relapsed/refractory CLL treated with ibrutinib-based regimens, in a multivariate analysis, only complex karyotype was significantly associated with inferior event-free survival (EFS; $P = .006$), whereas fludarabine-refractory CLL ($P = .005$) and complex karyotype ($P = .008$) were independently associated with inferior OS.[25] In another analysis of 308 patients treated with ibrutinib on four sequential clinical trials, in a multivariate analysis, complex karyotype at baseline, presence of del(17p), and age <65 years were all independently associated with a risk for CLL progression.[29] In patients ≥65 years without complex karyotype or del(17p), the estimated cumulative incidence of CLL progression at 4 years was 2% compared to 44% in patients <65 years with complex karyotype and del(17p).

Recent reports suggest that *BTK* and *PLCG2* mutations are associated with resistance to ibrutinib.[29,30] Among patients with relapsed CLL after treatment with ibrutinib, acquired *BTK* and/or *PLCG2* mutations were detected in 85% of patients at an estimated median of 9 months before relapse.[29] The reported variant allele frequencies (VAF) are variable with often low VAF associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance. *BTK* and/or *PLCG2* mutations have also been detected in patients with progressive CLL during ibrutinib therapy up to 15 months before the manifestation of clinical progression.[30] These findings suggest that testing for these mutations may be helpful to confirm ibrutinib resistance. Testing for mutations as screening for resistance is not currently recommended.

Early progression of disease (POD) within 2 years of first-line therapy has been identified as a clinical prognostic factor for inferior clinical outcomes in patients with CLL.[31] In an analysis of 829 patients, early POD after

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first-line treatment was associated with unfavorable-risk cytogenetics (del[11q]/del[17p]) and inferior ORR to first-line treatment. The ORR was 53% for those with early POD compared to 80% and 84%, respectively, for those with late POD and no POD. Early POD was also associated with inferior OS across all patients and in patients treated with FCR and bendamustine plus rituximab ($P < .05$).

Recurrent mutations in *NOTCH1*, *SF3B1*, and *BIRC3* genes with prognostic implications have been identified in approximately 4% to 15% of patients with newly diagnosed CLL and the incidences are much higher (15%–25%) in patients with CLL refractory to fludarabine.[32-37] *NOTCH1* mutation is also independently associated with Richter's transformation.[38,39] 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.[40-42] 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.[41] 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.[42] 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.[19] Collectively, the above studies suggest that the prognostic significance of these mutations may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated. Although these prognostic factors may provide useful prognostic information, the impact of these mutations relative to treatment with newer targeted therapies is uncertain. Treatment initiation or selection of treatment options should not be driven by these factors.

Among the flow cytometry-based prognostic parameters (CD38, CD49d, and ZAP-70), CD49d appears to be the strongest predictor of OS and treatment-free survival.[43-47] Increased expression of CD49d (≥30%) is associated with lymphadenopathy, progressive disease (advanced clinical stage, high serum lactate dehydrogenase, or beta-2-microglobulin levels), and aggressive disease biology [increased ZAP-70 or CD38, unmutated *IGHV*, trisomy 12, and lack of isolated del(13q)].[43,46,47] Expression of CD38 (≥7%)[7,11,13,48-50] and/or ZAP-70 (≥20%) are associated with shorter PFS and OS outcomes.[51-56] Both CD38 and ZAP-70 positivity correlate with unmutated *IGHV*, and were suggested as potential surrogate markers for *IGHV* mutational status.[7,51,52] 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.[57] Similarly, discordant results between ZAP-70 positivity and *IGHV* mutational status were reported in 20% to 25% of cases.[13,54] 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.[54-56] 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.[58-60] CD49d, CD38, and ZAP-70 expressions can be determined using flow cytometry or immunohistochemistry (IHC). However, standardization and reproducibility of these markers across laboratories remains a challenge. Evaluation of CD49d, CD38, and ZAP-70 is not recommended outside the context of clinical trials.

An elevated level of serum beta-2 microglobulin was shown to be a strong independent prognostic indicator for treatment-free interval, response to treatment, and OS in patients treated with first-line

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chemoimmunotherapy regimens.[61,62] In a multivariable analysis that included baseline beta-2 microglobulin, stage of disease, fludarabine-refractory disease, and del(17p), failure to achieve normalized beta-2 microglobulin at 6 months of treatment was associated with inferior PFS for patients on ibrutinib-based treatment.[62] One of the advantages of beta-2 microglobulin is that it is readily measured by standard laboratory evaluation of blood samples. However, it is influenced in a CLL disease-independent manner by renal dysfunction.

Several prognostic models incorporating multiple clinical and prognostic markers have been developed for the risk stratification.[63-69]

A prognostic nomogram and a more simplified prognostic index were developed using age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes to help stratify patients with untreated CLL into 3 different risk groups (low, intermediate, and high).[63] The estimated median survival times were not reached, 10 years, and 5 years, respectively, for the 3 risk groups. The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.[63] Several studies have independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in patients with untreated CLL, including those with early-stage (Rai stage 0) disease.[64,65]

Another multivariable model incorporating traditional and newer prognostic factors such as FISH cytogenetics, *IGHV* mutational status, and ZAP-70 expression was developed to estimate the probability of treatment (at 2 and 4 years) and time to first treatment.[66] 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.[66] This prognostic model may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention.

Integrated CLL Scoring System (ICSS) is a prognostic scoring system that stratifies patients into 3 risk groups (low, intermediate, and high) based on the cytogenetic abnormalities by FISH, *IGHV* mutational status, and CD38 expression.[68] International prognostic index for CLL (CLL-IPI) stratifies patients into 4 risk groups (low, intermediate, high, and very high) based on *TP53* and *IGHV* mutational status, serum beta-2 microglobulin concentration, clinical stage, and age.[69] The 5-year OS rates were significantly different between these risk groups (93%, 79%, 63%, and 23%, respectively). CLL-IPI also was validated in an independent cohort of patients with newly diagnosed CLL and was also useful for predicting time-to-first treatment.[70]

An integrated prognostic model including *NOTCH1*, *SF3B1*, and *BIRC3* mutations along with the cytogenetic abnormalities identified by FISH has been proposed to classify patients into 4 distinct prognostic subgroups: high-risk (*TP53* and/or *BIRC3* abnormalities); intermediate-risk [*NOTCH1* and/or *SF3B1* mutations and/or del(11q)]; low-risk (trisomy 12 and wild-type for all genetic lesions), and very low-risk [del(13q) only].[67] The 10-year survival rates for the 4 subgroups were 29%, 37%, 57%, and 69%, respectively.

Response Criteria

The response criteria set forth in the 1996 National Cancer Institute-sponsored Working Group (NCI-WG) guidelines are used in most clinical trials.[71] These response criteria were revised by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) to reflect recent advances in our understanding of newer prognostic markers, diagnostic parameters, and treatments.[72] In particular, the IWCLL guidelines provide further recommendations for the evaluations

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and response assessments appropriate for the general clinical practice setting versus for clinical trials.[72] In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters (as outlined below).

Complete response (CR): All of the following criteria must be met for a CR, ≥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). Confirmation of CR requires bone marrow evaluation with aspirate and core biopsy, demonstrating <30% lymphocytes, with no B lymphoid nodules.

Partial response (PR): At least 2 of the following criteria must be met for a PR for ≥2 months duration: ≥50% reductions in peripheral blood lymphocyte counts (from baseline); lymphadenopathy (based on sum of the products of multiple affected nodes); hepatomegaly; and/or splenomegaly. In addition, at least 1 of the blood counts should be normalized or increase by ≥50% from baseline, for at least 2 months duration.

Progressive disease comprises any of the following: ≥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).

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 the evidence of disease progression after ≥6 months 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.

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.

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.[73]

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.[74]

The use of Bruton's' tyrosine kinase (BTK) inhibitors (ibrutinib and acalabrutinib) and phosphatidylinositol 3-kinase (PI3K) inhibitors (idelalisib and duvelisib) 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.[75-77] 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

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patients likely to progress early.[75] Considering these findings, for patients receiving BTK inhibitors (ibrutinib or acalabrutinib) or PI3K inhibitors (idelalisib or duvelisib), the revised response criteria proposed by Cheson et al allow for a new response category, "PR with lymphocytosis," to include those with a clinical response (reduction in lymph nodes and splenomegaly) with persistent lymphocytosis (in the absence of other indicators of progressive disease).[73]

Minimal residual disease (MRD) negativity determined in the peripheral blood after the end of treatment is emerging as an important predictor of treatment efficacy, supporting the use of MRD for response evaluation.[78,79] In the combined analysis of two randomized phase III studies of the German CLL Study Group (GCLLSG) (CLL8 and CLL10), among patients who achieved CR and PR, 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).[78] The persistence of post-treatment splenomegaly as a sole abnormality in MRD-negative patients did not have a negative impact on PFS. MRD-negativity at end of treatment after first-line chemoimmunotherapy with FCR also correlated with longer PFS.[79] The median PFS was not reached for patients with undetectable MRD status at end of treatment compared to 38 months for those with detectable MRD ($P < .001$). MRD level (≤1% vs. >1%) after 3 courses of FCR predicted greater likelihood of achieving undetectable MRD status by end of treatment (64% vs. 9%, $P < .001$). PFS was significantly longer for patients with MRD ≤1% versus >1% after 3 courses of FCR (median 73 months vs. 41 months, $P < .001$), but similar for <0.01% versus 0.01%–1%.

Diagnosis

The diagnosis of CLL requires the presence of at least 5 x 10^9/L monoclonal B-lymphocytes in the peripheral blood and the clonality of B-cells should be confirmed by flow cytometry.[80] The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with less than 5 x 10^9/L B-lymphocytes in the peripheral blood.[80] B-cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when effacement of the lymph node architecture is observed in biopsy samples.

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

Distinguishing CLL/SLL from mantle cell lymphoma (MCL) is essential, as they are both CD5+ B-cell tumors. Though CD23 is often helpful, absence of cyclin D1 expression is critical in this differentiation of tumor types. CD200 and LEF1 are also useful markers to distinguish CLL from MCL.[81-84] Evaluation of cyclin D1 (flow cytometry or IHC) or FISH analysis for t(11;14), flow cytometry evaluation of CD200, and IHC for LEF1 may be helpful in the differential diagnosis of CLL.

FISH for the detection of del(11q), del(13q), trisomy 12, del(17p), stimulated metaphase karyotype, *TP53* sequencing, and molecular genetic analysis (by polymerase chain reaction [PCR] or sequencing) to detect *IGHV* mutation status can provide useful prognostic information and may guide selection of therapy. Expression of CD38, CD49d, and ZAP-70

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expression by flow cytometry, methylation, or IHC have been proposed as surrogate markers for *IGHV*-mutation status. *IGHV* mutation status determination is preferred over these surrogate markers.

Conventional metaphase cytogenetics is difficult in CLL as a result of the very low *in vitro* proliferative activity of the leukemic cells. Therefore, interphase cytogenetic analysis with FISH is the standard method to detect specific chromosomal abnormalities that may have prognostic significance. CpG oligonucleotide stimulation can be utilized to enhance metaphase cytogenetics.[85,86] A prospective study conducted by CLL Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens; moreover, the clonal abnormalities revealed by CpG-stimulated metaphase cytogenetics are consistent with that detected by interphase cytogenetic analysis with FISH and are reproducible among different cytogenetic laboratories.[86]

Monoclonal B-cell lymphocytosis

An absolute monoclonal B-lymphocyte count of <5 x 10^9/L in the absence of palpable lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder (eg, anemia or thrombocytopenia) is defined as monoclonal B-cell lymphocytosis (MBL).

MBL is a relatively recent diagnostic category describing individuals who present with an abnormal B-cell population with immunophenotype of CLL but do not meet the diagnostic criteria for CLL.[87,88] MBL is further categorized into low-count MBL (<0.5 x 10^9/L) that rarely progresses to CLL and high-count MBL (>0.5 x 10^9/L) that progresses to CLL requiring therapy at a rate of 1% to 2% per year.[89,90] High-count MBL is distinguished from Rai 0 CLL based on whether the monoclonal B-cell count is above or below 5 x 10^9/L.[91] A nodal variant characterized by nodal infiltration of CLL-line cells without apparent proliferation centers and absence of lymphadenopathy, has also been described in a subset of patients with MBL.[92]

MBL is associated with favorable molecular characteristics, mutated *IGHV* and del(13q), lower prevalence of del (11q)/del (17p) and mutated *TP53*, slower lymphocyte doubling time, longer treatment-free survival, and very low rate of progression to CLL.[88] Observation is recommended for all individuals with MBL.

Workup

The workup for CLL/SLL is similar to the workup for other lymphoid neoplasms. Quantitative immunoglobulins may be informative in patients with recurrent infections. Measurement of beta-2 microglobulin may provide useful prognostic information.[63] 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 monitor disease progression in patients with new symptoms when peripheral adenopathy is not present. However, serial CT scans are not recommended for asymptomatic patients. Reticulocyte counts and a direct Coombs test should be performed to evaluate for the possibility of hemolysis and pure red cell aplasia (PRCA) in patients with anemia. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.[93,94] Bone marrow biopsy ± aspirate could be useful in certain circumstances prior to initiation of treatment.

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Localized SLL (Lugano stage I)

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

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

Early-stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. In the absence of disease symptoms, a "watch and wait" approach is often appropriate for patients with stage II-IV SLL, low-risk CLL (Rai stage 0 or Binet A), or intermediate-risk CLL (Rai stage I-II or Binet B) and treatment will be beneficial if they become symptomatic or show evidence of progressive disease.[80] Patients with advanced-stage or high-risk CLL (Rai stage III-IV or Binet C) with progressive cytopenia require treatment. Selected patients with mild, stable cytopenia may continue to be observed.

Indications for initiating treatment include severe fatigue, weight loss, night sweats, and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); progressive anemia or thrombocytopenia; autoimmune anemia; or thrombocytopenia unresponsive to corticosteroids.[80] 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.[80]

In patients with indications for initiating treatment, patient age, performance status or fitness, and the presence or absence of del(17p) or *TP53* mutation should then help to direct treatment options, as discussed below. Re-evaluation for *TP53* mutation status, del(17p) by FISH, and *IGHV* mutation status (important for selection of initial treatment when considering chemoimmunotherapy) are recommended prior to initiating treatment in patients with indications for treatment. CpG-stimulated karyotyping is useful to identify high-risk patients, particularly for treatment with ibrutinib.

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

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

An oral formulation of fludarabine was investigated and is approved by the FDA for the treatment of patients with CLL (whose cancer has not responded to or progressed after treatment with at least one alkylating agent).[95-97] 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.

Rituximab and hyaluronidase human injection for subcutaneous use is approved by the FDA for the treatment of patients with previously untreated and previously treated CLL based on the results of the SAWYER trial in which subcutaneous rituximab (rituximab with recombinant human hyaluronidase) had similar pharmacokinetic characteristics as IV rituximab when used in combination with fludarabine and cyclophosphamide.[98] Rituximab and hyaluronidase human injection

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for subcutaneous use may be used in patients who have received at least one full dose of intravenous rituximab.

Re-challenge with the same anti-CD20 monoclonal antibody (MAB) is not recommended in patients experiencing severe reactions (eg, mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis) to a chosen anti-CD20 MAB. There are some data (based on clinical experience) showing that substitution with an alternative anti-CD20 MAB is tolerated in patients experiencing severe reactions to a specific anti-CD20 MAB; however, it is unclear if such a substitution poses the same risk of recurrence.[99,100]

Assessment of Functional Status and Comorbidity

CLL/SLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. Comorbidities are frequently present in older patients. In addition, organ function and bone marrow reserve also decline with advancing age. In a study that assessed the comorbidity burden and investigated its impact on treatment in 555 patients with untreated CLL enrolled in two GCLLSG trials, 26% of patients had comorbidities involving the metabolic/endocrine system, 21% of patients had comorbidities in the vascular system, and 12% of patients had cardiac comorbidities.[101] The presence of multiple comorbidities (≥2 comorbidities) was an independent predictor of clinical outcome independent of patients' age or disease stage.[101] The median OS (72 vs. 90 months; $P < .001$) and PFS (21 vs. 32 months; $P < .01$) were significantly shorter for patients with ≥2 comorbidities than for those with less than 2 comorbidities. In a multivariate analysis, after adjustment for other prognostic factors and treatment, comorbidity maintained independent prognostic value. These findings underscore the need to assess comorbidities, in addition to patient age and performance status, prior to treatment selection.

Cumulative Illness Rating Scale (CIRS), Charlson Comorbidity Index, and the NCI Comorbidity Index are some of the scoring systems that can be used to assess comorbidities in patients with CLL. CIRS in combination with creatinine clearance (CrCl) was used by the GCLLSG to assess the overall fitness of patients enrolled in clinical trials.[101,102]

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.[103] 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.[104] Based on these data, the panel decided to change the age cutoff from 70 years to 65 years.

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

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

First-line Therapy: Preferred Regimens

Ibrutinib

The efficacy and safety of ibrutinib monotherapy in patients ≥65 years with untreated CLL or SLL without del(17p) has been established in 2 phase III

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randomized trials, first demonstrated in the RESONATE-2 study [105,106] and more recently in the Alliance North American Intergroup Study (A041202).[107]

In the RESONATE-2 study, 269 patients (≥65 years of age) were randomized to receive ibrutinib or chlorambucil as first-line therapy.[105,106] After a median follow-up of 29 months, ibrutinib resulted in significantly higher overall response rate (ORR; 92% vs. 36%; *P* < .0001) and significantly longer PFS (89% vs. 34% at 24 months; *P* < .0001) compared to chlorambucil.[106] The PFS rates for ibrutinib were 97% and 89% respectively for patients with del(11q) and unmutated *IGHV*. With 41% of patients switching to ibrutinib, the estimated 2-year OS rates in the intent-to-treat population were 95% and 84%, respectively, for patients treated with ibrutinib and chlorambucil.[106]

In the Alliance North American Intergroup Study (A041202) that compared ibrutinib monotherapy (n =182) versus ibrutinib + rituximab (n =182) versus bendamustine + rituximab (BR; n = 183) in patients ≥65 years with untreated CLL, ibrutinib monotherapy and ibrutinib + rituximab resulted in superior ORR and PFS compared to BR.[107] The ORRs were 93% and 94%, respectively, for ibrutinib and ibrutinib + rituximab compared to 81% for BR. With a median follow-up of 38 months, the estimated 2-year PFS rates were 87% and 88%, respectively, for ibrutinib monotherapy and ibrutinib + rituximab compared to 74% for BR (*P* < .001 for both ibrutinib vs. BR and ibrutinib + rituximab vs. BR). The estimated 2-year PFS rates were also higher for ibrutinib and ibrutinib + rituximab among patients with complex karyotype (91% and 87%, respectively, compared to 59% for BR). The 2-year OS rates, however, were not significantly different among the treatment arms (90%, 94%, and 95%, respectively, for the 3 treatment arms; *P* = .87).

Ibrutinib monotherapy was approved for first-line therapy for all patients based on the results of the RESOANTE-2 study that established the efficacy of ibrutinib monotherapy as first-line therapy only in patients ≥65 years without del(17p).[105,106] The panel consensus was to continue the listing of ibrutinib with a category 1 recommendation for frail patients with significant comorbidity (not able to tolerate purine analogs) and for patients ≥65 years or younger patients with significant comorbidities.

The E1912 study (discussed on MS-16) showed that ibrutinib + rituximab was more effective than FCR for patients ≤70 years without del(17p)/*TP53* mutation, especially in patients with unmutated *IGHV*.[108] These results suggest that ibrutinib may be an appropriate option (instead of chemoimmunotherapy) for younger patients with unmutated *IGHV* who do want to enroll in a clinical trial. Therefore, based on the results of the E1912 study, the panel consensus was to change the recommendation of ibrutinib from a category 2A to category 1 recommendation for patients <65 years without del(17p) or *TP53* mutation.

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

Venetoclax + obinutuzumab

In recent clinical studies, venetoclax and obinutuzumab resulted in high response rates and undetectable MRD in patients with previously untreated CLL.[109,110] The CLL14 study evaluated venetoclax + obinutuzumab vs chlorambucil + obinutuzumab (fixed-duration treatment with 12 cycles of venetoclax 400 mg daily or chlorambucil in combination with obinutuzumab for first 6 cycles) for previously untreated CLL in 432 patients with comorbidities (CIRS score >6 and/or an estimated creatinine clearance <70 mL/min; 216 patients in each treatment group).[110] At a median follow-up of 29 months, venetoclax + obinutuzumab resulted in superior ORR (85% vs. 71%; *P* =.0007), CR rate (46% vs. 22%) and PFS (HR 0.35; *P* <.0001) compared to chlorambucil + obinutuzumab. The undetectable-MRD rate ($<10^{-4}$ as assessed by allele-specific oligonucleotide polymerase chain reaction assay) at 3 months after

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completion of treatment was significantly higher with venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab in both peripheral blood (76% vs 35%; *P* < .0001) and bone marrow (57% vs 17%; *P* < .0001).[110] The undetectable-MRD rate at 12 months after completion of treatment was 81% and 27%, for venetoclax + obinutuzumab and chlorambucil + obinutuzumab, respectively. Undetectable-MRD status at 3 months after completion of treatment correlated with longer PFS. Venetoclax + obinutuzumab was also associated with low rate of conversion to MRD-positive status 1 year after treatment. Venetoclax was recently granted broad FDA-approval for the treatment of patients with untreated and relapsed/refractory CLL.

The panel consensus was to include venetoclax + obinutuzumab as a preferred regimen with a category 2A recommendation for frail patients with significant comorbidity (not able to tolerate purine analogs) and patients ≥65 years or younger patients with significant comorbidities.

First-Line Therapy: Other Recommended Regimens

Bendamustine + Anti-CD20 Monoclonal Antibody

In a multicenter phase II trial (CLL2M study), the BR regimen induced high response rates (ORR, 88%; CR, 23%) in patients with previously untreated CLL (n = 117; 26% of patients were older than 70 years), with similar response and survival outcomes among the subgroup of elderly patients (age >70 years).[111] After a median observation time of 27 months, the median PFS for all patients was 34 months, and OS rate was 90.5%. Thrombocytopenia (22%), neutropenia (20%), anemia (20%), allergic/infusion reactions (9%), and infections (8%) were the most common grade 3 or 4 toxicities.

In the ongoing phase III randomized trial (MABLE study) that is evaluating rituximab and chlorambucil (R-chlorambucil; n = 120) and BR (n = 121) as first-line treatment for CLL in patients who are not candidates for fludarabine-based chemoimmunotherapy (older age or the presence of comorbid conditions), BR was associated with higher CR rate (24% vs. 9%; *P* = .002) and significantly longer median PFS (40 months vs. 30 months; *P* = .003) than R-chlorambucil.[112] The ORR was similar for BR and R-chlorambucil (91% vs. 86%; *P* = .304). The median OS was not significantly different between the two groups (44 months vs. not reached). The median follow-up was 24 months. The incidence of adverse events was similar between treatment groups, but the incidence of grade 3 adverse events was higher for BR compared to R-chlorambucil (75% and 64%, respectively). The updated results of the CLL10 study (discussed below) also confirmed that BR is associated with a decreased risk of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).[113] After a median follow-up of 58 months, the incidences of secondary AML and MDS were 3% and 1% in FCR and BR arms, respectively.

In the CLL10 study that compared BR and FCR as first-line therapy for CLL without del(17p), there was no significant difference in PFS between the treatment groups for patients >65 years, although the PFS benefit of FCR was significant in physically fit patients <65 years.[113] The incidence of severe neutropenia and infections were significantly more frequent in the FCR arm, especially among patients >65 years. In a phase II study that included 44 patients with untreated CLL (median age 63 years; 13 patients were ≥70 years), bendamustine in combination with ofatumumab resulted in an ORR of 95% (43% CR).[114] With a median follow-up of 29 months, the median PFS was not reached and the estimated 28-month PFS rate was 72%. The regimen was well tolerated with 89% of patients receiving all 6 cycles and grade 3/4 adverse events were reported in 57% of patients.

A phase II study evaluating bendamustine with obinutuzumab in patients with previously untreated CLL (n = 102) also reported an ORR of 89% (49% CR), after a median follow-up of 11 months.[115] Neutropenia was the

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most common grade 3 or 4 adverse event (27%), and the incidence of grade 3 or 4 infections was reported in 12% of patients. In the subgroup analysis of 158 patients who received bendamustine and obinutuzumab in the GREEN study, after a median follow-up of 33 months, the ORR was 81% (35% CR) and the estimated 2-year PFS rate was 82%.[116] Neutropenia, infections, infusion-related reactions, and tumor lysis syndrome (TLS) were the most common grade 3/4 adverse events reported in 53%, 20%, 17%, and 8% of patients, respectively. Careful TLS risk assessment, pretreatment, and monitoring is required in patients receiving bendamustine and obinutuzumab.

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

Chlorambucil + Anti-CD20 Monoclonal Antibody

The results of the CLL11 study established that chlorambucil plus obinutuzumab is superior to chlorambucil plus rituximab for elderly patients and for those with comorbidities lacking del(17p) or *TP53* mutation.[117,118] In this study, 781 patients with comorbid conditions (defined as CIRS score >6 or an estimated CrCl of 30–69 mL/min) were randomized to receive chlorambucil (n = 118), chlorambucil plus obinutuzumab (n = 333), or chlorambucil plus rituximab (n = 330).[117] The combination of chlorambucil with obinutuzumab or rituximab resulted in significant improvement in the median PFS compared to chlorambucil monotherapy (27 months, 16 months, and 11 months, respectively, for chlorambucil plus obinutuzumab, chlorambucil plus rituximab, and chlorambucil alone; $P < .001$).[117] The survival benefit was seen in all of the subgroups except in patients with del(17p). After the median follow-up of 48 months, the median PFS (29 months vs. 15 months; $P < .001$) and median time to next treatment (43 months vs. 33 months; $P < .0001$) were significantly longer for chlorambucil plus obinutuzumab compared to chlorambucil plus rituximab.[118] Neutropenia (35%), infusion-related reactions (21%), thrombocytopenia (11%), and infections (11%) were the frequent grade 3 or higher toxicities with chlorambucil plus obinutuzumab. Neutropenia (28%) and infections (14%) were the most frequent grade ≥3 toxicities associated with chlorambucil plus rituximab.

The results of the iLLUMINATE study demonstrated ibrutinib + obinutuzumab as a more effective first-line therapy than chlorambucil + obinutuzumab for patients ≥65 years and for patients <65 years with comorbidities (median age was 71 years; ibrutinib + obinutuzumab, n = 113; chlorambucil + obinutuzumab, n = 116).[119] At a median follow-up of 31 months, ibrutinib + obinutuzumab resulted in superior (independent review committee [IRC]-assessed) PFS (median not reached vs. 19 months; $P < .0001$) and higher (IRC-assessed) ORR (88% vs. 73%) compared to chlorambucil + obinutuzumab. In the high-risk population, the ORRs were 90% (14% CR) and 68% (4% CR), respectively. The estimated PFS rate at 30 months was 79% and 31%, respectively, for ibrutinib + obinutuzumab and chlorambucil + obinutuzumab. The PFS benefit with ibrutinib + obinutuzumab was observed across all subgroups of patients [unmutated *IGHV*: not reached vs. 15 months; del(17p): not reached vs. 11 months]. The 30-month OS rate was not significantly different between the treatment arms (86% and 85% for ibrutinib + obinutuzumab and chlorambucil + obinutuzumab, respectively). Pneumonia (5%), atrial fibrillation (4%), febrile neutropenia (4%), and pyrexia (4%) were the most common adverse events in the ibrutinib + obinutuzumab arm. Infusion-related reactions (7%), febrile neutropenia (6%), pneumonia (4%), TLS (4%), and pyrexia (3%) were more common with chlorambucil + obinutuzumab. Infusion-related reactions were less frequent with ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab (any grade, 25% vs. 58%; grade ≥3, 3% vs. 9%).

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

The safety and efficacy of chlorambucil plus ofatumumab as a first-line treatment for patients with untreated CLL who were not candidates for fludarabine-based therapy due to advanced age and/or comorbidities was confirmed in a multicenter phase III study (COMPLEMENT 1; 447 patients were randomized to chlorambucil plus ofatumumab vs. chlorambucil monotherapy).[120] After a median follow-up of 29 months, the median PFS was significantly longer for ofatumumab plus chlorambucil compared to chlorambucil monotherapy (22 months vs. 13 months; *P* < .001). The median OS was not reached in both arms. Ofatumumab plus chlorambucil also resulted in higher ORR (82% vs. 69%, *P* = .001) and superior CR rate (12% vs. 1%) compared to chlorambucil alone. Chlorambucil plus ofatumumab is indicated for the treatment of previously untreated CLL in patients for whom fludarabine-based therapy is considered inappropriate.

Chlorambucil plus ofatumumab or rituximab is included with a category 2A recommendation for frail patients with significant comorbidity and patients ≥65 years or younger patients with significant comorbidities. Chlorambucil plus ofatumumab would be an appropriate treatment option for patients who are not candidates for fludarabine-based therapy due to advanced age and/or comorbidities.[120] Chlorambucil plus rituximab should be reserved for patients who cannot tolerate obinutuzumab.[121,122]

Fludarabine, Cyclophosphamide, and Rituximab

The 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*.[21,113,123]

In the CLL8 study, 817 physically fit patients with previously untreated CLL (median age 61 years) were randomized to receive up to 6 courses of either the FCR (n = 408) or FC (n = 409) regimen.[21] The FCR regimen resulted in higher ORR (90% vs. 80%; *P* < .001) and CR rate (44% vs. 22%; *P* < .001) compared with FC. After a median follow-up of 6 years, the median PFS was 57 months and 33 months, respectively, for FCR and FC (*P* < .001). The median OS was not reached for FCR and was 86.0 months for FC (*P* = .001). FCR was associated with a statistically significant survival benefit compared to FC in patients <65 years (5-year OS rates were 81% and 69%, respectively; *P* = .002). The corresponding 5-year OS rates were 74% and 62%, respectively, in patients ≥65 years (*P* = .288). The incidence of prolonged neutropenia was significantly higher with the FCR regimen than with FC during the first year after treatment (17% vs. 9%; *P* = .007).

In a phase II study of 300 patients with previously untreated CLL, at a median follow-up of 13 years, the ORR was 95% (72% CR).[123] The overall 13-year PFS rate was 31% (54% for patients with mutated *IGHV* and 9% for patients with unmutated *IGHV*). MRD negativity was achieved in 51% of patients with mutated *IGHV,* with a PFS rate of 80% at 13 years. In a multivariable analysis, unmutated *IGHV* and del(17p) by conventional karyotyping were significantly associated with inferior PFS. Long-term PFS was notable particularly for patients with mutated *IGHV*, with a plateau on the PFS curve beyond 10 years.

The final analysis of the CLL10 study confirmed the superiority of FCR over BR as first-line therapy for CLL without del(17p) in fit patients (n = 567; CIRS score ≤6, CrCl >70 mL/min).[113] The median age was 62 years, but a significantly higher proportion of patients were >65 years in the BR arm (39% vs. 30%). After a median follow-up of 37 months**,** the ORR was 95% for FCR and 96% for BR (*P* = 1.0) with no difference in OS (3-year OS rate was 91% for FCR vs. 92% for BR; *P* = .89). FCR resulted in

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higher CR rate (40% vs. 31%), more MRD negativity (59% vs. 26% at 12 months; *P* < .0001; 55% vs. 27% at 18 months; *P* = .002), and longer median PFS (55 months vs. 42 months; *P* = .0003) compared to BR. The PFS benefit of FCR was significant in physically fit patients <65 years and in patients with mutated *IGHV*. The median PFS was 54 months and 39 months, respectively, for FCR and BR in patients ≤65 years (*P* = .0004) and there was no significant difference in PFS between the treatment groups for patients >65 years (median not reached for FCR and 49 months for BR; *P* = .172). Among patients with a mutated *IGHV,* the median PFS was not reached for FCR compared to 55 months for BR (*P* = .089). The incidence of severe neutropenia and infections were significantly more frequent in the FCR arm (39% vs. 25%), especially in patients older than 65 years.

The E1912 study showed that ibrutinib + rituximab was more effective than FCR for patients ≤70 years without del(17p)/*TP53* mutation (354 patients were randomized to ibrutinib and rituximab; 175 patients were randomized to FCR).[108] With median follow-up of 33 months, ibrutinib + rituximab was associated with significantly improved PFS (HR = 0.35; *P* <.0001) and OS (HR = 0.168; *P* = .0003) compared to FCR. In subgroup analysis for PFS, ibrutinib + rituximab was more effective than FCR, especially for patients with unmutated *IGHV* (HR = 0.26; *P* < .0001) but ibrutinib + rituximab was not superior to FCR in patients with mutated *IGHV* (HR = 0.44; *P* = .07). The incidences of grade 3 to grade 5 myelosuppression (neutropenia [44% vs. 23%], anemia [12% vs. 3%], and thrombocytopenia [14% vs. 3%]), neutropenic fever (16% vs. 2%), and infection (8% vs. 5%) were higher with FCR, whereas the incidences of atrial fibrillation (3% vs. 0%), hypertension (7% vs. 2%), and diarrhea (3% vs.1%) were higher with ibrutinib.

Based on the results of the E1912 study, the panel consensus was to change the recommendation of FCR from category 1 (preferred regimen) to category 2A (other recommended regimen) for patients <65 years without significant comorbidities. The panel emphasizes that FCR remains an appropriate first-line therapy option for patients <65 years without significant comorbidities, especially in those with mutated *IGHV*.

Fludarabine Plus Rituximab

Fludarabine with concurrent or sequential administration of rituximab was evaluated in the CALGB 9712 study in patients with untreated CLL.[20,124] 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).[124] 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%.[20] 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.[125]

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

HDMP Plus Rituximab

In a small cohort of patients with previously untreated CLL (n = 28; median age was 65 years), high-dose methylprednisolone (HDMP) plus rituximab resulted in a 96% ORR with CR in 32% of patients. At a median follow-up of 36 months, the median PFS was 31 months and OS rate was 96%.[126] In the small subgroup of patients aged >70 years (n = 8), the ORR was 100% and 3 patients achieved a CR (38%). HDMP plus rituximab was associated with a lower risk of myelosuppression and

Discussion Update in Progress

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lower incidences of infectious complications (attributed to treatment in the frontline setting, good performance status of the patients, use of anti-infective prophylaxis during treatment, and the administration of intravenous immunoglobulin [IVIG] to patients with infections and hypogammaglobulinemia).

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

Ibrutinib + anti-CD20 Monoclonal Antibody

The results of recent randomized phase III trials demonstrated that ibrutinib + anti-CD20 MAB (rituximab or obinutuzumab) is more effective than chemoimmunotherapy with BR (Alliance North American Intergroup Study) or chlorambucil + obinutuzumab (iLLUMINATE study) for untreated CLL without del(17p) or *TP53* mutation in patients ≥65 years and for patients <65 years with comorbidities.[107,119] The E1912 study also showed that ibrutinib + rituximab was more effective than FCR for patients ≤70 years without del(17p)/*TP53* mutation, especially for those with unmutated *IGHV*.[108] Ibrutinib + obinutuzumab was recently approved by the FDA for first-line therapy based on the results of the iLLUMINATE study.[119]

However, the majority of the panel members acknowledged that ibrutinib + anti-CD20 MAB has not yet demonstrated improvement in clinical outcomes compared to ibrutinib monotherapy in a randomized clinical trial. In addition, the panel members also noted that in the Alliance North American Intergroup Study (A041202), the addition of rituximab to ibrutinib was not associated with improved clinical outcomes compared to ibrutinib monotherapy (the estimated 2-year PFS rates were 88% and 87%, respectively, for ibrutinib + rituximab and ibrutinib monotherapy; *P* = .49).[107] The consensus was that the longer PFS was more the result of continuous and indefinite ibrutinib therapy, than due to the contribution of an anti-CD20 MAB during the first 6 months of treatment. Improved outcomes with addition of an anti-CD20 MAB may more likely be seen with fixed duration treatment with this regimen.

Ibrutinib + obinutuzumab (for frail patients with significant comorbidity and patients age ≥65 y and younger patients with significant comorbidities) and ibrutinib + rituximab (for patients <65 y without significant comorbidities) are included as a category 2B (other recommended regimens).

Venetoclax + Obinutuzumab

The CLL14 study established the efficacy of this combination only in patients with comorbidities (CIRS score >6 and/or an estimated creatinine clearance <70 mL/min).[110] The panel members acknowledged that the efficacy of this combination for patients without significant comorbidities has not been established in a randomized clinical trial. However, with the recent FDA approval, some panel members agreed that this combination may be an appropriate fixed-duration chemoimmunotherapy-free treatment option for younger patients without comorbidities who do want to enroll in a clinical trial. Therefore, the consensus of the panel was to include venetoclax + obinutuzumab with a category 2B recommendation for patients <65 years of age without significant comorbidities.

Pentostatin, Cyclophosphamide, and Rituximab

Pentostatin, cyclophosphamide, and rituximab (PCR) also has demonstrated activity in patients with untreated CLL.[127,128] However, the PCR regimen does appear to provide an advantage over FCR in terms of efficacy or toxicity.[129] In a community-based, multicenter, phase III randomized trial (n = 184) that compared the safety of PCR with the FCR regimen in patients with previously untreated (80% of patients) or minimally pretreated CLL, the ORRs were similar for PCR and FCR (49% vs. 59%), but the CR rate was lower in the PCR group (7% vs. 14%; *P* = .04).[129] The incidence of grade 3 or 4 infectious events and neutropenia

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were similar between treatment arms, with increased incidence of leukopenia and thrombocytopenia in the FCR group.[129]

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

Monotherapy with anti-CD20 Monoclonal Antibody or Chlorambucil

The efficacy of obinutuzumab monotherapy in previously untreated CLL at two different doses (1000 mg vs. 2000 mg) in 80 patients with intact organ function and ECOG PS <3 was evaluated in a phase II study.[130] 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.[130] Infusion-related reaction was the most frequent grade 3 or 4 adverse event in both treatment arms. Additional studies are warranted to determine the durability of response and long-term side effects of obinutuzumab monotherapy in patients with untreated CLL.

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

With multiple randomized studies showing a survival advantage for combination regimens containing chlorambucil or rituximab compared to monotherapy with either of these agents, the majority of the panel members acknowledged that monotherapy with chlorambucil or rituximab is not an effective first-line treatment even for frail patients with comorbid conditions. However, some panel members felt that given the favorable tolerability profile, monotherapy with rituximab or chlorambucil may be an appropriate treatment option for a small fraction of very frail patients or patients ≥65 years with substantial comorbidities or decreased performance status for whom more intensive regimens are not appropriate.[131,132]

Monotherapy with rituximab or chlorambucil is included with a category 3 recommendation.[131,132]

Relapsed or Refractory Therapy: Preferred Regimens

Ibrutinib, venetoclax plus rituximab (VenR), duvelisib, and idelalisib plus rituximab are included as options for patients with relapsed or refractory disease, regardless of patient's age and comorbidities.

Ibrutinib and VenR are included with a category 1 recommendation, based on the results of the phase III randomized studies (RESONATE and MURANO, respectively).[133,134] Although the panel acknowledged that duvelisib and idelalisib plus rituximab are preferred treatment options based on the efficacy data (in terms of median PFS) from randomized phase III studies,[135,136] the panel consensus was to include duvelisib and idelalisib plus rituximab with a category 2A recommendation due to their toxicity profile (colitis, diarrhea, and increased risk of infections).

Ibrutinib

The safety and efficacy of ibrutinib in relapsed/refractory CLL/SLL was established in a phase III randomized study (RESONATE); 391 patients with previously treated CLL were randomized to monotherapy with ibrutinib (420 mg once daily) or ofatumumab.[133] The updated results of this study also confirmed that ibrutinib significantly improved ORR, PFS, and OS compared to ofatumumab in patients with relapsed/refractory CLL/SLL who had received at least one prior therapy.[137,138] At a median follow-up of 44 months, the median PFS (not reached vs. 8 months for ofatumumab; *P* < .0001) and 3-year PFS rates (59% vs. 3%) were significantly better for ibrutinib.[138] At the time of this analysis, with 68% of patients randomized to ofatumumab crossing over to ibrutinib, the ORR and 3-year OS rates were 91% and 74%, respectively, for ibrutinib. Major hemorrhage, grade ≥3 atrial fibrillation, and grade ≥3 hypertension occurred in 6%, 6%, and 8% of patients, respectively, and the incidence of most of the grade ≥3

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adverse events (neutropenia, pneumonia, and atrial fibrillation) decreased with 4-year follow-up.

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

Venetoclax Plus Rituximab

The results of a phase III randomized study (MURANO) demonstrated that VenR (n = 194) is associated with superior outcomes compared to BR (n = 195) in patients with relapsed/refractory CLL.[134] After a median follow-up of 24 months, ORR (92% vs. 72%; *P* < .0001) and the 2-year PFS rate (85% vs. 36%) were significantly higher for VenR than for BR. The 2-year PFS was also higher for VenR than for BR among patients with del(17p) (82% vs. 28%) as well as for those without del(17p) (86% vs. 41%). The rate of clearance of MRD from peripheral blood samples was higher for VenR than for BR (62% vs. 13%) and the rate was also higher for VenR than for BR at any time during the trial (84% vs. 23%). The incidence of grade 3 or 4 neutropenia (58% vs. 39%) and grade ≥3 TLS (3% vs. 1%) were higher with VenR.

See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of TLS associated with venetoclax.

Duvelisib

Duvelisib was recently approved by the FDA for the treatment of relapsed/refractory CLL and SLL based on the results of the phase III randomized DUO study and the DYNAMO study.[135,139,140]

In the DUO study, 319 patients with relapsed/refractory CLL/SLL were randomized to either duvelisib (n = 160) or ofatumumab (n = 159).[135] Patients who had received prior treatment with BTK or PI3K inhibitors were excluded. With a median follow-up of 22 months, duvelisib resulted in significantly improved lymph node response (>50% reduction in lymph node burden; 85% vs. 16%), higher ORR (74% vs. 45%; *P* < .0001), and longer median PFS (13 months vs. 10 months; *P* < .0001) compared to ofatumumab. At the time of follow-up, the median OS was not significantly different between the treatment arms (not reached with an estimated 1-year OS rate of 86% in both treatment arms). Grade ≥3 adverse events including neutropenia, diarrhea, pneumonia, and colitis were reported in 30%, 15%, 14%, and 12% of patients, respectively. The efficacy of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL was established in the DUO crossover extension study (90 patients crossed over to duvelisib following disease progression on ofatumumab).[139] The ORR after crossover to duvelisib was 77% compared to 29% on ofatumumab pre-crossover. In the subset of 47 patients with no response on ofatumumab pre-crossover, the ORR after crossover to duvelisib was 73%. The median PFS was 15 months for patients who crossed over to duvelisib compared to 9 months on ofatumumab pre-crossover.

In the phase II study (DYNAMO) evaluating the safety and efficacy of duvelisib in 129 patients with relapsed or refractory indolent NHL (28 patients with relapsed/refractory SLL), duvelisib resulted in an ORR of 47% (68% for patients with SLL).[140] With a median follow-up of 12 months, the estimated median PFS was 10 months for the entire study population. Neutropenia (28%), anemia (12%), thrombocytopenia (13%), and diarrhea (15%) were the most common grade ≥3 adverse events.

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

Idelalisib Plus Rituximab

Idelalisib (the isoform-selective oral inhibitor of PI3K-delta) has demonstrated promising clinical activity in patients with relapsed or refractory CLL/SLL.[136,141] In the multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with

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either idelalisib (150 mg) or placebo.[136] The majority of the patients (78%) were ≥65 years, 40% had moderate renal dysfunction (CrCl, <60 mL/min), 35% had poor bone marrow function (grade 3 or higher cytopenias), and 85% had a CIRS score >6. At the first planned interim analysis, the study was stopped early owing to the overwhelming efficacy of idelalisib plus rituximab.[136] At 24 weeks, the PFS rate was 93% and 46% in the idelalisib group and placebo group, respectively. Among patients with relapsed CLL with coexisting conditions, idelalisib plus rituximab significantly improved ORR (81% vs. 13%; *P* < .001), PFS (not reached in the idelalisib group vs. 6 months in the placebo group), and OS at 12 months (92% vs. 80%; *P* = .02), compared to rituximab plus placebo. Grade 3 or 4 adverse events (pneumonia, pyrexia, and febrile neutropenia) were reported in 40% of patients in the idelalisib group and 35% in the placebo group. The second interim analysis of this study also confirmed the superior safety and efficacy of idelalisib plus rituximab in terms of ORR, PFS, and OS.[141] Idelalisib plus rituximab is an appropriate treatment option for relapsed/refractory CLL/SLL in patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or grade ≥3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).

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

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

Relapsed/Refractory Therapy: Other Recommended Regimens

Acalabrutinib

Acalabrutinib, a second-generation BTK inhibitor, demonstrated activity in patients with relapsed or refractory CLL.[77,142] In a phase II study of 134 patients with relapsed/refractory CLL, after a median follow-up of 20 months, the ORR was 85% (ORR including PR with lymphocytosis was 93%), the estimated median PFS was not reached, and the 18-month PFS rate was 88%.[142] Patients with ibrutinib intolerance have also been successfully treated with acalabrutinib without recurrence of symptoms.[143] In a cohort of 33 patients with ibrutinib intolerance, after a median follow-up of 10 months, the ORR (including PR with lymphocytosis) was 76% and the median PFS has not been reached. Headache, diarrhea, upper respiratory tract infection, fatigue, nausea, arthralgia and pyrexia, and weight increase were the most common adverse events of any grade observed in ≥20% of patients. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with acalabrutinib.

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

Alemtuzumab With or Without Rituximab

Alemtuzumab (subcutaneous or intravenous), either as monotherapy or in combination with rituximab, has demonstrated activity in patients with fludarabine-refractory CLL.[144-148] In a phase II study of 93 patients with fludarabine-refractory CLL, alemtuzumab monotherapy resulted in an ORR of 33% (CR, 2%).[144] The median time to progression was 4.7 months for all patients (9.5 months for patients whose cancer responded to treatment) and the median OS was 16 months (32 months for patients whose cancer responded to treatment).[144] The results of the CLL2H trial showed that subcutaneous alemtuzumab is also effective for the treatment

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of fludarabine-refractory CLL resulting in an ORR of 34%. At a median follow-up of 38 months, the median PFS, OS, and time to treatment failure (TTTF) were 8 months, 19 months, and 6 months, respectively.[145] In a retrospective analysis that included 202 patients with pretreated CLL, alemtuzumab was associated with a favorable ORR (32%), median PFS (6.2 months), and OS (21 months).[147] Myelosuppression and infections were the most common grade 3-4 toxicities. Alemtuzumab plus rituximab results in a higher ORR (53%) than that observed with alemtuzumab monotherapy and there was no significant difference in response rates between patients with fludarabine-sensitive and fludarabine-refractory disease.[148]

Alemtuzumab ± rituximab is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities. However, it should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.[144,147]

Bendamustine and Rituximab With or Without Idelalisib or Ibrutinib

In a phase II trial of GCLLSG, the BR regimen resulted in an ORR of 59% (CR rate, 9%) in patients with relapsed CLL (n = 78; median 2 prior therapies).[149] The ORR among the subgroup (n = 22) with fludarabine-refractory disease was 46%. After a median follow-up of 24 months, the median PFS and OS for all patients were 15 months and 34 months, respectively. The most common grade 3 or 4 adverse events included hematologic toxicities (50% of patients) and infections (13%; all grade 3 events).[149]

The results of recent phase III trials have shown that the addition of idelalisib or ibrutinib to BR significantly improves PFS in patients with relapsed or refractory CLL.[150,151] In the HELIOS trial that evaluated BR plus ibrutinib in 578 patients with previously treated CLL or SLL (≥18 years of age), PFS was significantly improved in patients treated with BR plus ibrutinib compared to those treated with BR plus placebo (not reached vs. 13 months; $P < .0001$).[150] The PFS at 18 months (as assessed by the IRC) was 79% and 24%, respectively. In a phase III randomized study of 416 patients with relapsed or refractory CLL (42% of patients were ≥65 years of age), at a median follow-up 14 months, the median PFS was 21 months for BR plus idelalisib versus 11 months for BR plus placebo ($P < .0001$).[151] The incidence of opportunistic infections and severe adverse events were more frequent in the idelalisib arm.

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

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

The results of the phase III randomized REACH trial confirmed that the addition of rituximab to fludarabine that compared FCR versus FC in patients with CLL at first relapse (n = 552; patients were excluded if they had received prior FC regimen or prior rituximab and patients were required to have fludarabine sensitive disease at relapse), FCR was associated with significantly improved median PFS (based on investigator assessment) compared with the FC arm (31 months vs. 21 months; $P < .001$), although OS was not significantly different between the treatment regimens.[152] 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 IRC were also significantly higher with the FCR regimen.

The final analysis of a phase II study that evaluated FCR in patients with relapsed or refractory CLL (n = 284; median 2 prior therapies) confirmed the safety and efficacy of this regimen in patients without high-risk features (refractory to prior therapy or chromosome 17 abnormalities).[153] 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

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56% of treatment cycles and grade 3 or 4 thrombocytopenia in 20% of cycles. Pneumonia or sepsis was reported in 16% of patients. The subgroup of patients with fludarabine-refractory disease (n = 54) had a significantly lower ORR (56% vs. 79%; *P* < .001) and CR rate (7% vs. 39%; *P* < .001) compared with fludarabine-sensitive patients; the median PFS (8 months vs. 28 months; *P* < .001) and OS (38 months vs. 52 months; *P* < .05) were also significantly decreased among patients with fludarabine-refractory CLL.[153] In addition, the subgroup of patients (n = 20) with chromosome 17 abnormalities (based on standard karyotyping) had worse outcomes with an ORR of 35% (no CR), median PFS of 5 months, and median survival of only 10.5 months. These findings suggest that FCR is a more appropriate treatment option for patients who have received fewer prior therapies (<4 prior regimens) and have fludarabine-sensitive disease, with no chromosome 17 abnormalities.[153]

The PCR regimen is also safe and effective in patients with previously treated CLL. In a small series of patients with relapsed or refractory CLL (n = 32), PCR resulted in an ORR of 75% among patients with fludarabine-refractory disease.[154]

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

Fludarabine, Cyclophosphamide, and Ofatumumab

In the COMPLEMENT 2 study that evaluated the combination of FC plus ofatumumab (n = 183) versus FC alone (n = 182) in patients with relapsed CLL (median age 61 years; 134 patients [37%] >65 years), FC plus ofatumumab was associated with improved PFS with a manageable safety profile. The median PFS (primary endpoint; assessed by the IRC) was 29 months and 19 months, respectively, for the combination of FC plus ofatumumab and FC (*P* = .0032).[155] There was no significant difference in OS between the treatment arms. The incidences of grade ≥3 adverse events were 74% and 69%, respectively, for the two treatment groups. Neutropenia was the most common adverse event reported in 49% of patients treated with FC plus ofatumumab and in 36% of patients treated with FC. Based on the results of this study, the FDA approved the combination of FC plus ofatumumab for the treatment of patients with relapsed CLL.

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

HDMP Plus Rituximab

In small studies, HDMP combined with rituximab was effective in patients with heavily pretreated CLL (including fludarabine-refractory disease), resulting in an ORR of 93% (CR in 14%–36% of patients) and a median PFS of 7 to 15 months.[156,157] 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.[156,157]

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

Idelalisib

In a phase I study of 54 patients with relapsed/refractory CLL, idelalisib monotherapy resulted in an ORR of 72% (39% PR and 33% PR with treatment-induced lymphocytosis). The median PFS was 16 months and the median OS was not reached, with 75% of patients surviving at 36 months.[76] 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

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refractory SLL.[158] The ORR was 55% (6 out of 11) and 61% (17 out of 28), respectively. The median duration of response was 2.3 months and 12.5 months, respectively. The median PFS was 4 months and 11 months, respectively.

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

Lenalidomide With or Without Rituximab

Lenalidomide monotherapy or in combination with rituximab has also shown activity in relapsed/refractory CLL.[159-161] In a phase II study of 59 patients with relapsed or refractory CLL, lenalidomide in combination with rituximab resulted in an ORR of 66% with CR in 12%.[159] The median OS was not reached, with an estimated 3-year OS rate of 71%. However, the ORR was lower for the subgroup of patients with fludarabine-refractory CLL compared with those with fludarabine-sensitive CLL (33% vs. 70%; *P* = .04). The most common grade 3 or 4 toxicity included neutropenia (74%), thrombocytopenia (34%), and infections or febrile episodes (24%). Tumor flare reactions (grade 1 or 2) occurred in 27% of patients. In the prospective, multicenter, randomized phase II trial of 103 patients with relapsed/refractory CLL (CLL-009 trial), at a median follow-up of 24 months, lenalidomide monotherapy resulted in an ORR of 40%. The median PFS and OS were 10 months and 33 months, respectively.[160] The median PFS and OS were significantly different between patients with CLL responding to lenalidomide and patients with stable disease (median PFS: 27 vs. 7 months, *P* < .001; median OS: not reached vs. 20 months; *P* = .011). Myelosuppression and tumor flare reactions were the most common grade 3 or 4 adverse events.

Lenalidomide with or without rituximab is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities. Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. A randomized phase III study (ORGIN trial) evaluating monotherapy with lenalidomide vs. chlorambucil as initial therapy for CLL in patients >65 years was halted by the FDA due to concerns for increased risk of death in the lenalidomide arm versus chlorambucil arm.[162] Lenalidomide is not recommended as initial therapy.

Obinutuzumab or Ofatumumab Monotherapy

The results of the GAUGIN study confirmed that obinutuzumab has monotherapy activity in patients with heavily pretreated relapsed or refractory CLL.[163] In this study of 20 patients, obinutuzumab at a fixed dose of 1000 mg resulted in a best ORR of 30%; median PFS and duration of response were 11 months and 9 months, respectively.

Ofatumumab has demonstrated activity in patients with bulky lymphadenopathy and fludarabine-refractory CLL.[164,165] In the final analysis of the pivotal international clinical trial (n = 207; 95 patients with fludarabine- and alemtuzumab-refractory CLL [FA-ref CLL] and 112 patients with fludarabine-refractory CLL with bulky lymphadenopathy [>5 cm; BF-ref CLL]), ofatumumab monotherapy resulted in an ORR of 49% in patients with FA-ref CLL and 43% in those with BF-ref CLL.[165] The median PFS was 5 months and 6 months, respectively, for patients with FA-ref CLL and BF-ref CLL. The median OS was 14 months and 17 months for the FA-ref and the BF-ref groups, respectively. The most common ≥ grade 3 adverse events were infections (24%) and neutropenia (12%). An ad hoc retrospective analysis of patients with FA-ref CLL (n = 96) and BF-ref CLL (n = 112) showed that ofatumumab was also effective and well tolerated in patients with FA-ref CLL and previous rituximab exposure.[166] The ORR was 43%, 44%, and 53%, respectively, for CLL with previous rituximab exposure, rituximab-refractory CLL, and rituximab-naive CLL. The median

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PFS was 5.3, 5.5, and 5.6 months, respectively, and median OS was 15.5, 15.5, and 20 months, respectively.

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

Venetoclax

Venetoclax monotherapy has also shown promising activity in patients with relapsed or refractory CLL after prior treatment with ibrutinib or idelalisib, resulting in an ORR of 65% and 67%, respectively.[167,168] The median PFS has not yet been reached, and the estimated 12-month PFS rate was 79% for patients with relapsed or refractory CLL after prior treatment with idelalisib.[168] The most common grade 3 or 4 adverse events were neutropenia, thrombocytopenia, anemia, and decreased lymphocyte count. In a recent retrospective analysis, the use of venetoclax following failure of ibrutinib was associated with better ORR (79%) when compared with idelalisib (ORR of 46%) and a trend towards improved PFS.[169]

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

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

First-line Therapy: Preferred Regimens

Ibrutinib

Enrollment in an appropriate clinical trial is recommended for patients with del(17p) CLL. In the absence of a clinical trial, ibrutinib is the preferred treatment option. In a phase II trial that included 35 treatment-naïve patients with del(17p)/*TP53* mutation (median age 62 years), at a median follow-up of 24 months, ibrutinib resulted in objective responses in 32 of 33 evaluable patients (55% of patients had a PR and 42% of patients had a PR with lymphocytosis) and the estimated OS at 24 months was 84%.[170] After a median follow-up of 57 months, the estimated 5-year PFS and OS were 74% and 85%, respectively.[171] 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.

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

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

Venetoclax + obinutuzumab

In the single arm, phase 1b dose-finding study that included 32 patients with previously untreated CLL, del(17p)/*TP53* mutation was present in 17% of patients and venetoclax + obinutuzumab resulted in an ORR of 100% (60% CR and 40% PR) in this subgroup of patients.[109] In the CLL14 study (discussed above) that demonstrated the efficacy of this combination in 432 patients with previously untreated CLL, del(17p) and *TP53* mutations were present in 8% and 7% of patients, respectively.[110] Venetoclax + obinutuzumab resulted in statistically significant improvement in PFS and significantly higher undetectable-MRD rate across all patients groups. The panel consensus was to include this combination as a preferred regimen with a category 2A recommendation.

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First-line Therapy: Other Recommended Regimens

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

Alemtuzumab With or Without Rituximab

Alemtuzumab, initially approved for fludarabine-refractory CLL, has also shown activity as a first-line treatment for patients with CLL.[172-175] In an international, multicenter, randomized phase III study (CAM307), 297 patients with previously untreated CLL were randomized to receive alemtuzumab or chlorambucil.[173] Alemtuzumab resulted in a significantly higher ORR (83% vs. 55%; $P < .0001$) and CR rate (24% vs. 2%; $P < .0001$) than chlorambucil and a modest but statistically significant survival benefit compared with chlorambucil (median PFS was 15 months vs. 12 months; $P = .0001$). Alemtuzumab was also associated with higher ORR (64% vs. 20%) and longer median PFS (11 months vs. 2 months) in the small subgroup of 21 patients with del(17p). After a median follow-up of 25 months, median OS was not reached for either treatment arm; no significant difference in survival was reported between treatment arms.[173] Infusion-related events, CMV infections, and grade 3 or 4 neutropenia (41% vs. 25%) were higher with alemtuzumab compared with chlorambucil.

HDMP Plus Rituximab

HDMP in combination with rituximab has demonstrated activity in a small cohort of 28 patients with previously untreated CLL with poor-risk factors at baseline (eg, high-risk Rai stage in 48%; unmutated *IGHV* in 57%; cytogenetic abnormalities in 39%, including del11q and del17p).[126]

Obinutuzumab Monotherapy

In the phase II study that demonstrated significant efficacy of obinutuzumab monotherapy in patients with untreated CLL (n = 80), del(17p) and del(11q) were present in 10% and 12% of patients, respectively.[130] Obinutuzumab monotherapy (at dose levels of 2000 mg and 1000 mg) resulted in an ORR rate of 67% and 49%, respectively.

Relapsed/Refractory Therapy: Preferred Regimens

Ibrutinib

The results of the RESONATE-17 phase II study confirmed the safety and efficacy of ibrutinib in 145 patients with relapsed or refractory del(17p) CLL.[176] At a median follow-up of 12 months, the ORR (as assessed by the IRC) was 83%. In an extended analysis with a median follow-up of 28 months, the investigator-assessed ORR and the 24-month PFS and OS rates were 83%, 63%, and 75%, respectively.[176] The subgroup analysis of the RESONATE study also showed that the presence of del(17p) or *TP53* mutation was not associated with inferior PFS outcomes.[137] The ORR and 18-month PFS rates were 89% and 71%, respectively, for patients with del(17p) compared to 91% and 79% for those without del(17p). The ORR and 18-month PFS rates were 91% and 66% for patients with *TP53* mutation compared to 92% and 81% for those without *TP53* mutation. The estimated 18-month OS rate was 83% for the del(17p) subgroup and 79% for those with complex karyotype.

Ibrutinib is included with a category 1 recommendation. See *Special Considerations for the Use of Small Molecule Inhibitors* for the management of toxicities associated with ibrutinib.

Venetoclax With or Without Rituximab

In a phase II study of 107 patients (61 patients ≥65 years; 46 patients <65 years) with relapsed or refractory del(17p) CLL, at a median follow-up of 12.1 months, venetoclax monotherapy resulted in an ORR of 79.4% as

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assessed by the IRC.[177] The ORR was also high (>70%) in all subgroups of patients with additional risk features [eg, fludarabine-refractory status, bulky disease, del(17p), *TP53* mutation]. The estimated 12-month PFS and OS rates were 72% and 87%, respectively. Neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%) were the most commonly treatment-related adverse events. Venetoclax is approved for the treatment of relapsed or refractory del(17p) CLL.

In the phase III randomized MURANO study that compared VenR and BR in patients with relapsed/refractory CLL, VenR was superior to BR in prolonging PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation.[134] Del(17p) and *TP53* mutation were present in 27% and 25% of patients, respectively, in patients randomized to VenR and in 27% and 28% of patients, respectively, in patients randomized to BR.

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

Duvelisib

In the phase III randomized study (DUO) that evaluated duvelisib for relapsed/refractory CLL (n = 319), del(17p), and/or *TP53* mutation were present in 31 out of 160 patients randomized to duvelisib.[135] The PFS advantage with duvelisib was maintained across all subgroups of patients, including those with del(17p) or *TP53* mutation. In the subgroup of patients with del(17p), the median PFS was significantly extended for duvelisib compared to ofatumumab (17 months vs. 9 months).[178]

Idelalisib Plus Rituximab

The second interim analysis of the phase III randomized study that evaluated idelalisib plus rituximab confirmed that this regimen also retained efficacy in patients with high-risk features such as del(17p) or *TP53* mutations [43% of patients had del(17p)/*TP53* mutation]; unmutated *IGHV*, ZAP-70, and CD38 expression; and beta-2 microglobulin (>4 mg/L).[141] At 12 months, the estimated PFS rate was 62% and the median OS was not reached for patients with del(17p) or *TP53* mutation or del(11q) compared to 74% and not reached for patients without any of these cytogenetic abnormalities.

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

Relapsed/Refractory Therapy: Other Recommended Regimens

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

Acalabrutinib

In the phase II study that evaluated acalabrutinib in relapsed/refractory CLL, acalabrutinib was associated with an ORR of 85% in patients with relapsed/refractory del(17p) CLL.[142] The median PFS was not reached and the 18-month PFS rate was 78%.

Alemtuzumab With or Without Rituximab

In the CLL2H trial that evaluated subcutaneous alemtuzumab for the treatment of fludarabine-refractory CLL, none of the poor-prognosis

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genetic abnormalities including del(17p) or *TP53* mutation were associated with significant differences in response rates or survival.[145] Among patients with del(17p) CLL, the median OS and TTTF were 18 months and 6 months, respectively. As discussed earlier, the addition of rituximab results in higher response rates than alemtuzumab monotherapy in patients with fludarabine-refractory CLL.[148]

HDMP Plus Rituximab

HDMP in combination with rituximab is also effective for relapsed CLL with unfavorable cytogenetic features [n = 27; 9 patients had del(17p)] resulting in objective responses of 78% of patients [including 5 out of 9 patients with del(17p), and the 3-year survival rate was 41%.[179] Infectious complications developed in 29% of patients, which may necessitate adequate antiinfective prophylaxis and close monitoring for early signs of infections.

Idelalisib

In a phase I study that evaluated idelalisib monotherapy in 54 patients with relapsed/refractory CLL with adverse characteristics, idelalisib monotherapy resulted in an ORR of 54% (7 out of 13 patients) in patients with del(17p) and/or *TP53* mutation and the median PFS was 3 months.[76]

Lenalidomide With or Without Rituximab

In the CLL-009 trial, lenalidomide monotherapy also showed modest activity resulting in an ORR of 22% and 36%, respectively, in patients with relapsed/refractory CLL with del(17p) and *TP53* mutation.[160] Although the ORR was lower for patients with del(17p) [22% vs. 47% for those without del(17p); *P* = .049], there were no significant differences in PFS (5 months vs. 11 months; *P* = .171) and OS (19 months vs. 35 months; *P* = .318) between these two groups.

Lenalidomide with rituximab also has modest activity resulting in an ORR of 53% in patients with relapsed/refractory del(17p) CLL, which was not significantly different from the ORR in patients without del(17p) (70%; *P* = .35). The TTTF was also not significantly different between the groups of patients with del(17p) and other cytogenetic risk features, although this subgroup analysis is limited by small subgroup size.[159]

Ofatumumab

In the international, multicenter study that evaluated ofatumumab monotherapy in patients with FA-ref CLL and BF-ref CLL, ofatumumab resulted in an ORR of 41% among patients with FA-ref CLL with del(17p).[164] However, the ORR was only 14% among patients with BF-ref CLL with del(17p). Among all characteristics evaluated, del(17p) was the only factor associated with lower response rate in patients with BF-ref CLL.

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

First-line Consolidation Therapy

The CLLM1 study demonstrated the feasibility and efficacy of lenalidomide maintenance after first-line chemoimmunotherapy.[180] In this study, 89 patients with a poor outcome after first-line chemoimmunotherapy [those who achieved at least a PR to first-line therapy with MRD levels of $\geq 10^{-2}$ or MRD levels of $\geq 10^{-4}$ to $<10^{-2}$ with either an unmutated *IGHV*, del(17p) or *TP53* mutation at baseline] were randomized to receive either lenalidomide maintenance (n = 60) or placebo (n = 29). After a median observation time of 18 months, the median PFS was 13 months in the placebo arm and was not reached in the lenalidomide arm. The incidences of treatment-related adverse events such as hematologic toxicity (50% vs. 17%), gastrointestinal disorders (61% vs. 28%), and skin disorders (63% vs. 28%) were more frequent with lenalidomide.

Lenalidomide maintenance after first-line chemoimmunotherapy is included as an option under *Other Recommended Regimens* for high-risk patients (MRD $\geq 10^{-2}$ or $\geq 10^{-4}$ and $<10^{-2}$ with unmutated *IGHV*).

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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.[181] 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 months, ofatumumab maintenance resulted in improved PFS compared to observation (29 months vs. 15 months; $P < .0001$). Neutropenia (24%) and infections (13%) were the most common grade ≥3 adverse events associated with ofatumumab maintenance. Ofatumumab maintenance is approved for patients with recurrent or progressive CLL who are in CR or PR after two or more lines of prior therapy.

The phase III randomized multicenter trial (CONTINUUM trial) demonstrated the feasibility and efficacy of lenalidomide maintenance after second-line therapy.[182] 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 32 months, the median PFS was significantly longer for lenalidomide compared to placebo (34 months vs. 9 months). There was no significant difference in OS between the two groups. Neutropenia (60% vs. 23%), thrombocytopenia (17% vs. 6%), and diarrhea (8% vs. <1%) were the most common grade 3 or 4 adverse events in the lenalidomide and placebo arms, respectively.

Lenalidomide maintenance (category 2A) or ofatumumab maintenance category 2B) are included as an options under *Other Recommended Regimens* for patients who are in CR or PR to second-line therapy.[181,182]

Allogeneic Hematopoietic Cell Transplant

Long-term results from several prospective studies have shown that allogeneic hematopoietic cell transplant (HCT) can provide long-term disease control and also overcome the poor prognosis associated with del(17p) and *TP53* mutations.[183-190] The results of the prospective multicenter trial (GCLLSG CLL3X study) showed that nonmyeloablative allogeneic HCT can provide long-term disease control in a significant proportion of patients with poor-risk CLL independent of the presence of *TP53*, *SF3B1*, and *NOTCH1* mutations.[188] 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.[188] 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).[190] The results of a recent systematic review/meta-analysis suggest that based on lower non-relapse mortality and slightly better OS rates, reduced-intensity conditioning regimens may be a more reasonable choice whenever allogeneic HCT is indicated.[191] The efficacy of myeloablative versus nonmyeloablative (reduced-intensity conditioning) regimens has not been evaluated in a randomized trial.

It is understood that studies involving allogeneic HCT are subject to significant selection biases. Nonetheless, based on the available evidence, prior to the development of small molecule inhibitors, allogeneic HCT was considered as an effective treatment option for patients with high-risk CLL (disease that is refractory to purine analog-based chemoimmunotherapy or disease relapse within 2 years after treatment with purine analog-based chemoimmunotherapy and/or disease with del(17p) or *TP53* mutation).[192] At the present time, given the favorable outcome of patients with del(17p) or *TP53* mutation treated with ibrutinib as first-line therapy and the availability of venetoclax as an effective treatment option for relapsed or refractory CLL with del(17p) or *TP53* mutation, allogeneic HCT is not considered as a reasonable

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treatment option for refractory CLL or disease relapse within 12 to 24 months after initial purine analogue-based therapy.[193]

Indications for Allogeneic HCT

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

For patients with CLL/SLL with del(17p) or *TP53* mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if complex karyotype (≥3 abnormalities) is present. However, available data suggest that complex karyotype (≥5 abnormalities) is associated with inferior OS and EFS following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics.[194]

Histologic Transformation and Progression

Histologic transformation (also known as Richter's transformation) to more aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma (HL) occurs in about 2% to 10% of patients during the course of their disease and treatment.[195-197] Unlike CLL, clinical outcomes in patients with histologic transformation are exceedingly poor with a pattern of no to minimal responses to chemoimmunotherapy regimens and a median survival of 5 to 8 months from diagnosis.[198]

The exact mechanism of Richter's transformation is not well understood; however, it has been associated with molecular characteristics of the patients' CLL and prior CLL-directed therapies. The following molecular characteristics have been associated with the risk of developing Richter's transformation and may be linked to the pathogenesis of the disease:[38,39,199-203]

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

The incidence of Richter's transformation increases with the number of prior chemoimmunotherapy regimens and the rate is higher in patients treated with a combination of purine nucleoside analogues and alkylating agents.[200] Richter's transformation has also been reported following treatment with the novel agents ibrutinib and venetoclax.[204-206] Unlike progressive CLL, Richter's transformation developing after treatment with ibrutinib lacked resistance to *BTK* and *PLCG2* mutations.[205] While the rate of Richter's transformation during venetoclax therapy was significantly higher among patients with heavily pretreated del(17p) CLL, it was less common among a broader group of patients with less heavily pretreated relapsed/refractory CLL.[206] Further study is needed to determine the exact risk profile and mechanism of Richter's transformation.

CLL with expanded proliferation centers (accelerated CLL) may be diagnosed when proliferation centers in CLL are expanded or fuse together and show a high Ki-67 proliferative rate (>40%). Progression to CLL with increased prolymphocytes (CLL-PLL) may occur when there are increased prolymphocytes in the blood (>10%–<55%). Neither of these findings is considered as Richter's transformation, but rather as progression of CLL, associated with a more aggressive disease course.[207]

Diagnosis and Workup

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

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The workup of patients with Richter's transformation or progression is similar to that of patients with CLL/SLL and should include history and physical exam with attention to node-bearing areas, including Waldeyer's ring, and the size of liver and spleen, whole body PET/CT scan, or chest/abdomen/pelvis CT with contrast of diagnostic quality. PET/CT scans are recommended to identify the optimal site for nodal biopsy, and biopsies should be directed to lesions with highest FDG uptake on PET scans.[208-210] A maximum standardized uptake value (SUVmax) ≥10 on PET scan has been shown to be a valid marker to distinguish Richter's transformation from CLL among patients not treated with kinase inhibitor therapy.[211] However, PET SUVmax ≥10 alone lacks both sensitivity and specificity to distinguish Richter's transformation from CLL in patients who develop Richter's transformation while on ibrutinib.[212] Tissue biopsy is required for the definitive diagnosis of Richter's transformation. PET alone is insufficient.

Epstein-Barr virus (EBV) infection has been reported in 16% of the patients with Richter's transformation and is associated with a poor outcome.[213] EBV infection of CLL can produce Reed-Sternberg (RS)-like proliferations, and presence of morphologic RS cells in a CLL background should not be considered as Richter's transformation. However, RS-like cells in a background of CLL may progress to classical HL in some patients.[214] Biopsy specimen should be evaluated for EBV infection using latent membrane protein 1 (LMP1) staining or in situ hybridization of EBV-encoded RNA (EBER-ISH).

DLBCL arising from CLL can either be clonally unrelated to CLL (78%) or clonally related to CLL (22%).[199,215] Richter's transformation to clonally unrelated DLBCL is characterized by a significantly lower prevalence of *TP53* disruption and a significantly longer median survival than clonally related DLBCL (62 months vs. 14 months).[199] The majority of patients with Richter's transformation to clonally related DLBCL carry unmutated *IGHV.*[215] Molecular analysis is useful to establish the clonal relationship between baseline CLL tumor cells and histologically transformed tumor cells. *IGHV* gene sequencing or clonal *IGHV* rearrangements can be used to establish the clonal relationship between CLL and histologically transformed tumor cells.[199,215]

Richter's transformation to DLBCL

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

For Richter's transformation to clonally related (or unknown clonal status) DLBCL, enrollment in a clinical trial is the preferred initial treatment option. In the absence of a suitable clinical trial, chemoimmunotherapy regimens recommended for DLBCL can be used; however, these regimens typically result in poor responses.[198] Elevated platelet counts, higher hemoglobin levels, lower beta-2-microglobulin levels, and lower LDH levels have been identified as independent predictors of higher response rates to chemoimmunotherapy.[198] However, the use of these prognostic variables for selection of therapy for Richter's transformation has not yet been established. Evidence (mostly from single arm phase I/II studies) to support the use of chemoimmunotherapy regimens for DLBCL arising from CLL are discussed below.

In a phase II trial conducted by GCLLSG that included 15 patients with Richter's transformation, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) resulted in an ORR of 67% (7% CR).[216] After a median follow-up of 69 months, the median PFS and OS were 10 months and 21 months, respectively. Hematologic toxicities and infections were the most common adverse events.

In a single-institution retrospective cohort study of 46 patients with Richter's transformation treated with R-EPOCH (rituximab, etoposide,

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prednisone, vincristine, cyclophosphamide, doxorubicin), the ORR was 39% (17 out of the 44 patients evaluable for treatment response).[217] After a median follow-up of 39 months, the median PFS and OS were 4 months and 6 months, respectively. Complex karyotype was associated with significantly shorter PFS and OS. The estimated 1-year OS rate was 71% for patients without a complex karyotype.

The modified R-hyperCVAD regimen (rituximab, cyclophosphamide, vincristine, liposomal daunorubicin, dexamethasone alternating with methotrexate and cytarabine) with growth factor support was also active in patients with Richter's transformation (n = 30), resulting in an ORR of 43% (27% CR) and the 1-year OS rate was 28%.[218] However, it was associated with significant toxicity (grade 3 neutropenia was the most common hematologic toxicity) and was not more effective than an alternate hyperCVAD regimen (did not include methotrexate, cytarabine, rituximab, or growth factor support) that was evaluated in an earlier study.[219]

OFAR regimen (oxaliplatin, fludarabine, cytarabine, and rituximab) at different dosing schedules has also been evaluated in patients with Richter's transformation. In a phase I-II trial that included 20 patients with Richter's transformation, OFAR regimen (increasing doses of oxaliplatin, fludarabine, cytarabine, and rituximab) resulted in an ORR of 50%.[220] The median response duration was 10 months. After a median follow-up of 9 months, the 6-month OS rate was 53% and the survival rate was higher for patients achieving CR or PR. A modified OFAR regimen with reduced-dose cytarabine resulted in an ORR of 39% (7% CR), in a phase I-II study that included 35 patients with Richter's transformation. With a median follow-up of 26 months, the median survival was 7 months and the 2-year OS rate was 20%.[221] Grade 3/4 neutropenia and thrombocytopenia were the most common hematologic toxicities occurring in 80% of patients with both schedules of OFAR regimen.

R-CHOP, R-EPOCH, R-hyperCVAD regimen, and OFAR are included as options for chemoimmunotherapy, based on available data from clinical trials discussed above.

Allogeneic HCT can be considered for patients with disease responding to initial chemoimmunotherapy.[198,222,223] In a non-randomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic HCT after achieving a CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo allogeneic HCT, or who underwent allogeneic HCT for relapsed or refractory Richter's transformation (75% vs. 27% and 21%, respectively; P = .019).[198] In a retrospective analysis that evaluated the outcome after autologous or allogeneic HCT in 59 patients with Richter's transformation, the 3-year estimated OS, relapse-free survival (RFS), and cumulative incidences of relapse and non-relapse mortality rates were 36%, 27%, 47%, and 26%, respectively, for allogeneic HCT and 59%, 45%, 43%, and 12%, respectively, for autologous HCT.[222] In a multivariate analysis, chemotherapy-sensitive disease and reduced-intensity conditioning were found to be associated with superior RFS after allogeneic HCT. Autologous HCT may also be appropriate for patients with disease responding to initial therapy but are not candidates for allogeneic HCT due to age, comorbidities, or lack of a suitable donor.[222]

There are no effective treatment options for patients with Richter's transformation refractory to chemoimmunotherapy. Clinical trial is the preferred treatment option if available. Preliminary data from ongoing clinical trials suggest that anti-programmed death 1 (PD1) monoclonal antibodies (nivolumab and pembrolizumab) have promising activity in patients with Richter's transformation.[224-226] In a phase I/II study that included 20 patients with Richter's transformation, nivolumab in combination with ibrutinib resulted in an ORR of 60% (CR, 5% and PR,

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55%).[225] The median PFS was 4 months. Diarrhea (31%), pyrexia, and fatigue (each 23%) were the most common treatment-related grade 1 or 2 adverse events. The incidence of grade 3 or 4 febrile neutropenia and anemia were reported in 5% and 20% of patients, respectively. In a phase II study of 25 patients (16 patients with relapsed CLL and 9 patients with Richter's transformation to DLBCL), the use of pembrolizumab as a single agent resulted in an objective response rate of 44% in patients with Richter's transformation. The median PFS and OS were 5 months and 11 months, respectively.[226] Treatment-related grade ≥3 adverse events were reported in 60% patients. Thrombocytopenia (20%), anemia (20%), neutropenia (20%), and dyspnea and hypoxia (8% each) were the most common grade 3 or 4 adverse events.

The panel acknowledged that there are limited published data supporting the use of nivolumab and pembrolizumab in patients with Richter's transformation refractory to chemoimmunotherapy or in patients with a del(17p)/*TP53* mutation and that additional data will be forthcoming. However, some panel members felt that given the unmet clinical need and the lack of effective treatment options, inclusion of PD1 monoclonal antibodies (nivolumab and pembrolizumab) as a treatment option is reasonable (based on the data discussed above) for patients with Richter's transformation refractory to chemoimmunotherapy (especially if considering allogeneic HCT). In addition, some panel members also pointed out that these agents would also be appropriate as an initial treatment option for patients with del (17p) or *TP53* mutation and for those who are unable to receive chemoimmunotherapy regimens. Few panel members felt that monotherapy with PD1 monoclonal antibodies (nivolumab or pembrolizumab) is not an effective treatment option for patients with relapsed or refractory Richter's transformation outside of a clinical trial citing a recent report in which the use of PD1 monoclonal antibodies for the treatment of relapsed/refractory Richter's transformation in a non-trial population (10 patients with biopsy-proven Richter's transformation to DLBCL and all patients had received prior therapy with Bruton's tyrosine kinase inhibitors) was associated with poor efficacy with a short TTTF.[227]

Nivolumab and pembrolizumab with or without ibrutinib is included as an option with a category 2B recommendation for patients unable to receive chemoimmunotherapy, patients with del (17p) or *TP53* mutation, or those with chemoimmunotherapy-refractory disease.

Richter's Transformation to Hodgkin Lymphoma

Richter's transformation to HL is clinically less aggressive than Richter's transformation to DLBCL but it is associated with a poor prognosis than de novo HL.[196,197,228] Richter's transformation to HL should be managed as outlined in the NCCN Guidelines for Hodgkin Lymphoma. ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) was the most commonly used regimen resulting in an ORR of 68% and achievement of CR to the ABVD regimen was the most important factor predicting survival of patients with Richter's transformation to HL.[229,230]

CLL-PLL or Accelerated CLL

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

Special Considerations for the Use of Small Molecule Inhibitors

Ibrutinib, acalabrutinib, idelalisib, and duvelisib cause early mobilization of lymphocytes into the blood resulting in a transient increase in absolute lymphocyte count in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks after initiating therapy and may persist for several weeks on

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treatment.[75] 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.[75]

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.[105] 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.[231]

Acalabrutinib was not associated with any grade ≥3 bleeding events; grade ≥3 hypertension and atrial fibrillation were observed in 3% and 2% of patients treated with acalabrutinib, respectively.[77,142] Headaches commonly observed with acalabrutinib early in treatment course typically resolve after 1 to 2 months of treatment and generally can be managed with analgesics (eg, acetaminophen) and caffeine supplements.

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

Hepatitis B virus (HBV) reactivation and invasive fungal infections have been rarely reported in patients treated with ibrutinib.[232,233] There currently are no sufficient data to recommended routine screening and prophylaxis.

Hepatotoxicity (transaminase elevations), severe diarrhea or colitis, infections, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib or duvelisib. Hepatotoxicity is a major concern in younger patients treated with idelalisib as first-line therapy.[234] Close monitoring of transaminase levels is essential and concurrent administration of idelalisib or duvelisib with other hepatotoxic drugs should be avoided.

Idelalisib and duvelisib are also associated with increased risk of opportunistic infections (PJP and CMV reactivation) and febrile neutropenia. The addition of anti-CD20 MAB or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia.[151] Herpes virus prophylaxis with acyclovir or equivalent, PJP prophylaxis with sulfamethoxazole trimethoprim or equivalent, and routine monitoring for early signs of infectious complications and CMV reactivation (as described below under *Supportive Care*) is recommended for patients receiving idelalisib or duvelisib. Close monitoring of cutaneous reactions and initiation of supportive care with emollients, antihistamines, or topical steroids is recommended for patients receiving duvelisib.

TLS was an important side effect of venetoclax therapy in early clinical trials. Initiation at lower dose (20 mg for one week) and gradual step-wise ramp-up over 5 weeks to target dose (400 mg daily) along with prophylaxis for TLS is recommended to mitigate the risk and frequency of TLS in patients receiving venetoclax.[235] Initiation and accelerated escalation of venetoclax (20–400 mg over 3 weeks) with close inpatient monitoring for TLS can be done to quickly regain disease control in a selected subgroup of patients with high tumor burden, rapid disease progression, or disease relapse after treatment with B-cell receptor inhibitor therapy.[167,236,237] This

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accelerated schedule has been explored in a small number of hospitalized patients, who received intensive monitoring and TLS prophylaxis. Additionally, continued BTK inhibition concurrent with initiation and escalation of venetoclax with discontinuation of BTK inhibitor after venetoclax dose escalation to 400 mg daily can be considered.[167,236,237] Growth factor support should be considered for patients with neutropenia. Dose reduction may be necessary for patients with persistent neutropenia and limited bone marrow involvement.

Supportive Care

Infections

Infectious complications are influenced by the progressive reduction in immunoglobulin levels (hypogammaglobulinemia) and are more common in patients with previously treated CLL.[238,239] Patients with heavily pretreated fludarabine-refractory CLL have high susceptibility to developing serious infections.[240]

IVIG is associated with a significant decrease in the occurrence of infections but with no improvement in OS outcome.[241-245] Monitoring IVIG levels and monthly administration of IVIG (0.3–0.5 g/kg to maintain nadir levels of approximately 500 mg/dL) is recommended for selected patients with serum IVIG <500 mg/dL and recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.

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

Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients.[246] All live vaccines should be avoided. Patients with CLL tend to have poor response to influenza vaccine and should be counseled to exercise care during influenza season even with vaccination. Protein and conjugate vaccines were shown to induce better responses than plain polysaccharide vaccines.[247,248]

Hepatitis B Virus Reactivation

HBV reactivation has been reported in patients treated with chemotherapy with or without immunotherapy agents.[249,250] HBV carriers have high risk of HBV reactivation. Fulminant hepatitis, hepatic failure, and death associated with HBV reactivation have occurred in patients receiving anti-CD20 MAB (rituximab, obinutuzumab, or ofatumumab)-containing regimens, including rituximab, obinutuzumab, or ofatumumab.[251] HBV reactivation has also been reported in patients treated with alemtuzumab, ibrutinib, and idelalisib. HBV prophylaxis and monitoring is recommended in high-risk patients receiving anti-CD20 MAB, alemtuzumab, purine analogs, ibrutinib, and idelalisib.

HBsAg and HBcAb testing is recommended for all patients receiving anti-CD20 MAB-based regimens. In individuals who test positive for HBsAg and/or HBcAb, baseline quantitative PCR for HBV DNA should be obtained to determine viral load. However, a negative baseline PCR does not preclude the possibility of reactivation. Patients receiving IVIG may be HBcAb positive as a consequence of IVIG therapy, although HBV viral load monitoring is recommended.[252]

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.[253,254] Lamivudine prophylaxis should be avoided due to the risks for the development of resistance.

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During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes positive, consultation with a hepatologist and discontinuation of anti-CD20 MAB is recommended. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of treatment.[255]

Cytomegalovirus Reactivation

Clinicians should be aware of the high risk of CMV reactivation in patients receiving fludarabine-based chemoimmunotherapy, idelalisib, or alemtuzumab. Monitoring for the presence of CMV viremia using quantitative PCR (at least 2–3 weeks) is an effective approach to the management of CMV reactivation.[256] Current practices for the management of CMV reactivation include the use of prophylactic ganciclovir if CMV viremia is present or the use of ganciclovir if the viral load is found to be increasing during therapy.[257,258] 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.[259,260] Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias.

Although direct antiglobulin test (DAT) was used for the diagnosis of AIHA, most patients with AIHA have negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA.[261] 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.[261-264] 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.[261,265] 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.[266] 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.[266]

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine,[267] and splenectomy should be used in steroid-refractory cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias.[268-274] Romiplostim and eltrombopag have shown promising results in the treatment of thrombocytopenia associated with ITP.[275-278] 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.[260] 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.[260]

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Tumor Flare Reactions

Tumor flare reaction associated with lenalidomide is typically observed as painful enlargement of lymph nodes, and may be accompanied by lymphocytosis, spleen enlargement, low-grade fever, rash, and/or bone pain. Tumor flare reactions have been reported in approximately 80% of patients with untreated CLL (although these reactions were limited to grade 1 or 2 events) and in approximately 30% to 60% of patients with relapsed or refractory CLL.[279-281] Tumor flare was more frequent among patients with enlarged (>5 cm) lymph nodes at baseline.[279] In patients with relapsed or refractory CLL, the 25 mg initial dose of lenalidomide used in patients with multiple myeloma resulted in excessive toxicity (tumor flare, tumor lysis, and myelosuppression).[282] 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 is associated with an acceptable tolerability profile in patients with relapsed or refractory CLL (n = 103).[160,283]

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

Venous Thromboembolism

Lenalidomide may also be associated with venous thromboembolism (VTE) in patients with CLL/SLL.[279,284] Prophylaxis with daily low-dose aspirin (81 mg daily) may be considered in patients with extremely high platelet counts at baseline. Patients already on anticoagulants, such as warfarin, do not need aspirin. However, it should be noted that these recommendations may differ from the NCCN Guidelines for Venous Thromboembolic Disease in which the recommendations for VTE associated with lenalidomide pertain only to patients with multiple myeloma.

Tumor Lysis Syndrome

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

Summary

The choice of first-line treatment for CLL/SLL should be based on the disease stage, presence or absence of del(17p) or *TP53* mutation, *IGHV* mutation status (if considering chemoimmunotherapy), patient's age, performance status, comorbid conditions, as well as the agent's toxicity profile. Ibrutinib is the preferred first-line therapy for all patients that offers excellent long-term disease control, including in high-risk subgroups such as those with del(11q) or del(17p)/*TP53* mutation and unmutated *IGHV*. Idelalisib is not indicated in first-line treatment. Chemoimmunotherapy with FCR is an appropriate first-line therapy option for fit patients <65 years with mutated *IGHV*, as it offers a defined treatment course and the majority of patients with mutated *IGHV* who receive first-line FCR are expected to have more than 10 years of PFS, and may potentially be cured of their disease. Ibrutinib, idelalisib (with or without rituximab), acalabrutinib, duvelisib, and venetoclax ± rituximab are effective treatment options for relapsed/refractory CLL/SLL.

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

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of histologic transformation will improve the clinical outcomes of patients with histologic transformation. Careful monitoring of adverse events after initiation of treatment and supportive care for the treatment-related complications should be an integral part of CLL/SLL management.

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