National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Version 4.2020 — December 20, 2019

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2020
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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

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

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 4.2020 of the NCCN Guidelines for CLL/SLL from Version 3.2020 include:

MS-1

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

Updates in Version 3.2020 of the NCCN Guidelines for CLL/SLL from Version 2.2020 include:

CSLL-D 1 of 6

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

- **First-line therapy for both, "Frail patient with significant comorbidity..." and "Patients aged <65 y without significant comorbidities"**
  - **"Acalabrutinib ± obinutuzumab" was added as a category 2A, preferred recommendation.**

CSLL-D 3 of 6

CLL/SLL with del(17p)/TP53 mutation

- **First-line therapy, "Acalabrutinib ± obinutuzumab" was added as a category 2A, preferred recommendation.**

CSLL-F

Special considerations for the use of small-molecule inhibitors

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

Continued

Updates in Version 2.2020 of the NCCN Guidelines for CLL/SLL from Version 1.2020 include:

CSLL-D

- **The footnote, "FDA-approved biosimilar is an appropriate substitute for rituximab" was removed from FCR only and added for all rituximab indications.**

Updates in Version 1.2020 of the NCCN Guidelines for CLL/SLL from Version 5.2019 include:

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CSLL-1

- **Monoclonal B-cell lymphocytosis (MBL)**
  - **5th bullet was added: "No organomegaly"**
  - **6th bullet was added: "No constitutional symptoms"**
- **Footnote c was revised: "Absolute monoclonal B lymphocyte count <5000/mm^3 *that persists more than 3 months* in the absence of..."**

CSLL-2

- **Useful Under Certain Circumstances:**
  - **7th bullet was revised: "Unilateral bone marrow aspirate + biopsy ~~at initiation of therapy~~" and corresponding footnote was added, "May be informative for the diagnosis of immune-mediated or disease-related cytopenias."**
  - **8th bullet was revised: "Hepatitis B *or C* testing if treatment contemplated."**
- **Footnotes**
  - **Footnote f was revised: "...CT scans may be warranted for *the evaluation of* symptoms ~~of or to evaluate~~ *of* bulky disease ~~*or*~~ *for the assessment of risk for TLS prior to initiating venetoclax*."**
  - **Footnote g was added, "May be informative for the diagnosis of immune-mediated or disease-related cytopenias."**

CSLL-3

- **Evaluate for indications for treatment**
  - **7th bullet was added: "Steroid-refractory autoimmune cytopenias."**
- **Indication present**
  - **"(if not previously done)" was added to *IGHV* mutation status.**
- **Footnotes**
  - **Footnote l was revised: "Absolute lymphocyte count alone ~~is~~ *or symptoms related to leukocytosis* are not an indication for treatment ~~unless above 200–300 x 10^9/L or symptoms are related to leukostasis~~. *Leukostasis is rarely seen in patients with CLL*." (Also for CSLL-4 and CSLL-5)**
  - **Footnote was removed: "Given incurability with conventional therapy, consider including clinical trial as first-line therapy."**

CSLL-4

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

- **After first-line therapy, treatment options based on "Response to Therapy" were added.**
  - **Response: "Continue treatment with B-cell receptor (BCR) pathway inhibitor until progression or Observation if treated with chemoimmunotherapy or targeted therapy with fixed-duration treatment until indication for retreatment as listed on CSLL-3."**
  - **No response pathway is directed to re-evaluate.**
- **Footnote q reference was updated: "~~Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931~~. 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." (Also for CSLL-5)**

CSLL-5

CLL/SLL with del(17p)/*TP53* mutation

- **Response to Therapy**
  - **Treatment option after response was revised from "Continue treatment with small molecule inhibitor" to "Continue treatment with BCR pathway inhibitor until progression or Observation, if treated with targeted therapy with fixed duration treatment."**
- **Footnote u was revised, "Patients with low ~~positivity~~ *percentage of del17p-positive cells* should be retested due to chance of false-positive results.**

CSLL-A

- **Footnote a was revised: "This table provides useful prognostic information ~~relative to the time to progression, where therapy is required, and survival~~ *for survival and time to progression in patients who received treatment.*"**

CSLL-C 1 of 4

- **Anti-infective prophylaxis**
  - **2nd bullet was revised: "...Some clinicians use ganciclovir (oral or IV) *pre-emptively* ~~prophylactically~~ if viremia is present..."**

Continued

Updates in Version 1.2020 of the NCCN Guidelines for CLL/SLL from Version 5.2019 include:

CSLL-C 3 of 4

- Autoimmune Cytopenias
  - 3rd primary bullet was revised: "Pure red cell aplasia (PRCA): ~~Evaluate~~ *Consider* bone marrow evaluation and for parvovirus B19, ~~and~~ herpes virus, *and* drug effects"
- Rituximab Rapid Infusion and Subcutaneous Administration
  - 1st bullet was revised: "If no *severe* infusion reactions were experienced with prior cycle of rituximab..."
  - 2nd bullet was added: "~~Rituximab hycela subcutaneous is acceptable alternative after initial IV dose~~. 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."

CSLL-D 1 of 6

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

- Significant comorbidities was clarified as "creatinine clearance [CrCl] <70 mL/min)."
- CLL/SLL without del(17p)/TP53 mutation, First-line therapy, Frail patient with significant comorbidity....
  - Other recommended regimens, 2nd bullet was revised: "Chlorambucil + obinutuzumab ~~+ anti-CD20 monoclonal antibody~~" and corresponding footnote was removed, "Obinutuzumab is superior to rituximab."
- First-line therapy, Patients aged <65 y without significant comorbidities
  - Venetoclax + obinutuzumab was moved from other recommended regimen to preferred regimen and changed from a category 2B recommendation to a category 2A recommendation.
  - Other recommended regimens, the qualifier to FCR, "preferred for patients with IGHV-mutated CLL" was moved from a footnote to be included here.

CSLL-D 2 of 6

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

- Relapsed/Refractory therapy for all patients, acalabrutinib was moved from other recommended regimen to preferred regimen and changed from a category 2A recommendation to a category 1 recommendation.

CSLL-D 3 of 6

CLL/SLL with del(17p)/TP53 mutation

- Relapsed/Refractory therapy, acalabrutinib was moved from other recommended regimen to preferred regimen and changed from a category 2A recommendation to a category 1 recommendation.
- Post first-line and second-line maintenance options were removed.

CSLL-D 4 of 6

- Footnote k was added for FCR, "FDA-approved biosimilar is an appropriate substitute for rituximab."
- Footnote m was revised, "Minimal residual disease (MRD) evaluation with a sensitivity of 10^{-4} according to the standardized ERIC method *or standardized next-generation sequencing (NGS) method.*"
- Footnote n was revised, "Acalabrutinib ~~should not be used~~ *has not been shown to be effective* for ibrutinib-refractory CLL with BTK C481S mutations."

CSLL-E

- The table, "Response Definition After Treatment for CLL/SLL" was updated based on reference, "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."
- MRD assessment was added.

CSLL-F

- Duvelisib toxicity, 5th bullet was revised, "Infections: PJP prophylaxis with sulfamethoxazole/trimethoprim or equivalent *is recommended during treatment and until the absolute CD4+ T-cell count is >200 cells/μL.*
- Ibrutinib toxicity, 4th bullet regarding ventricular tachyarrhythmias was added.
- Venetoclax toxicity, 2nd bullet regarding renal function was added.

Histologic Transformation (Richter's) and Progression

HT-2

- Workup, Useful in Selected Cases
  - 3rd bullet, hepatitis C was added.
  - 5th bullet was added, "Discussion of fertility issues and sperm banking."

HT-3

- Footnote k was added, "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."

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.

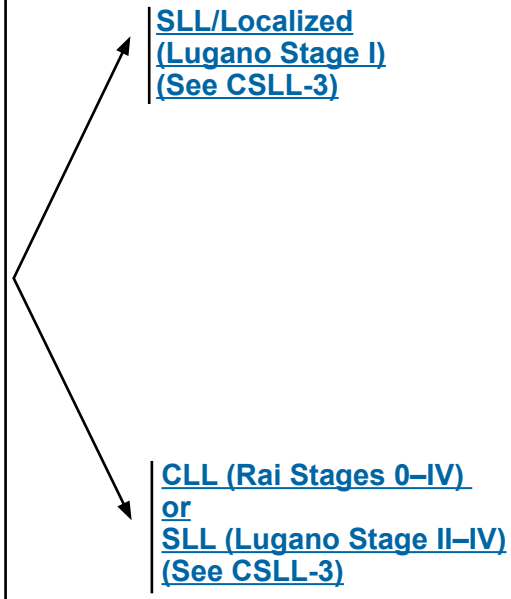
Note: All recommendations are category 2A unless otherwise indicated.

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

WORKUP

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

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **Quantitative immunoglobulins**
- **Reticulocyte count, haptoglobin, and direct Coombs' test**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated[f]**
- **Beta-2-microglobulin**
- **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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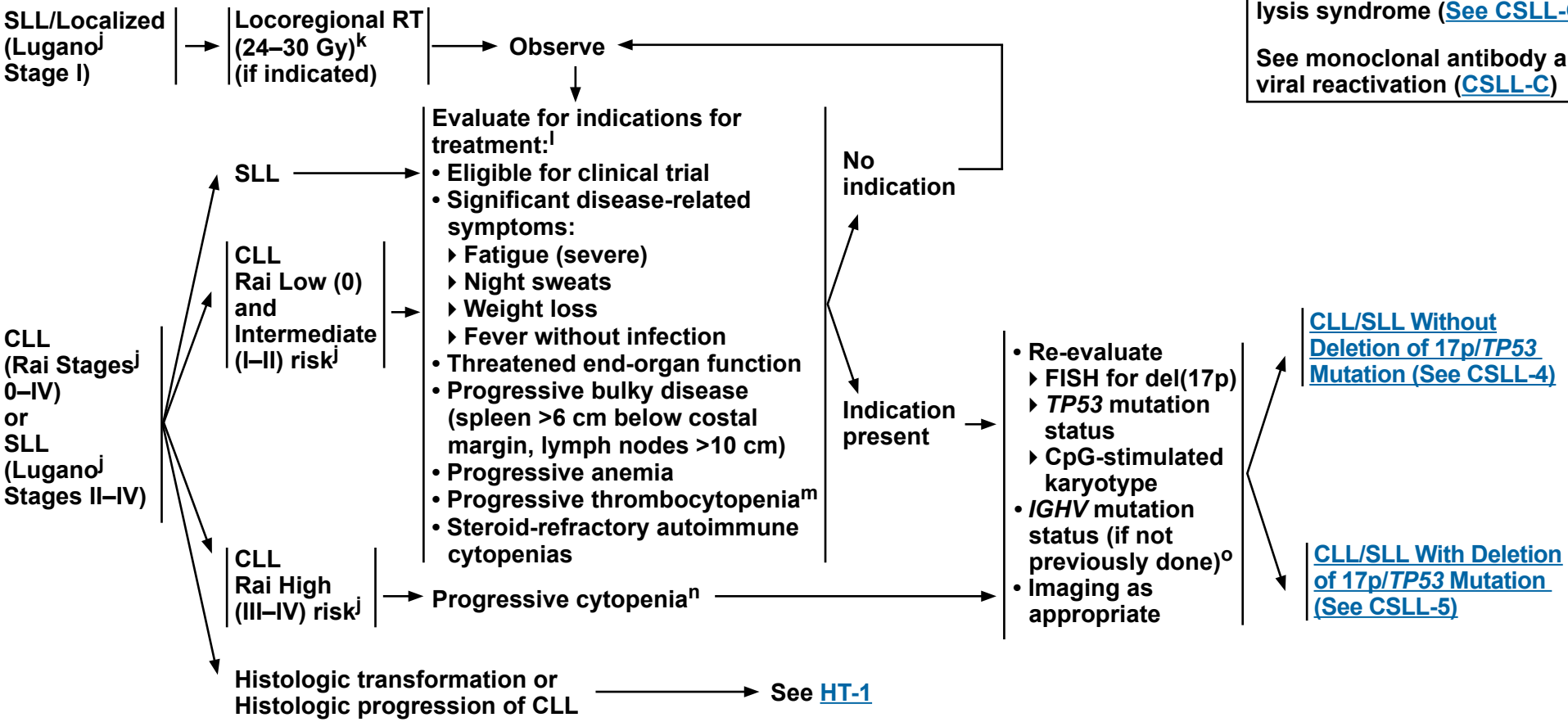
PRESENTATION[i]

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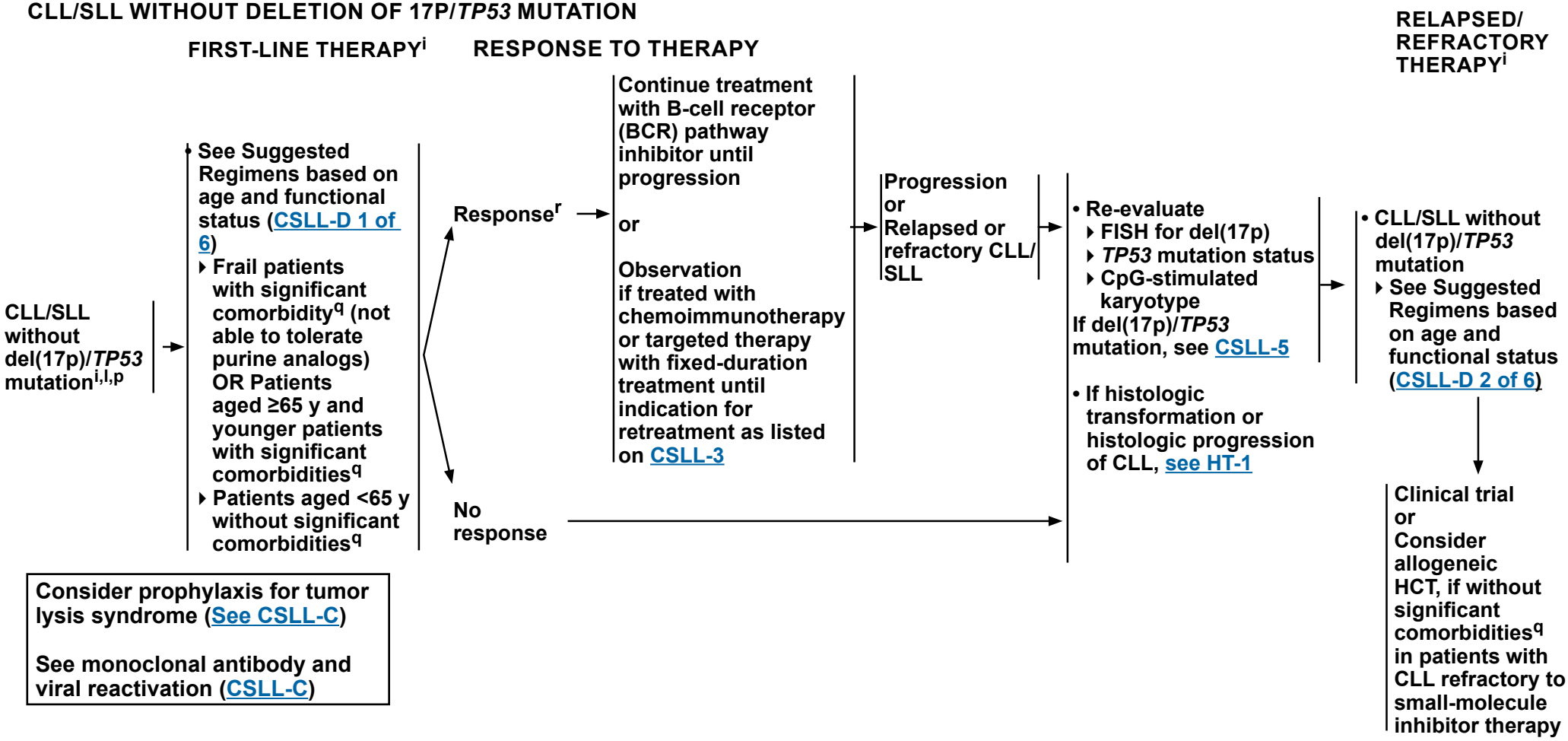
CLL/SLL WITHOUT DELETION OF 17P/*TP53* MUTATION



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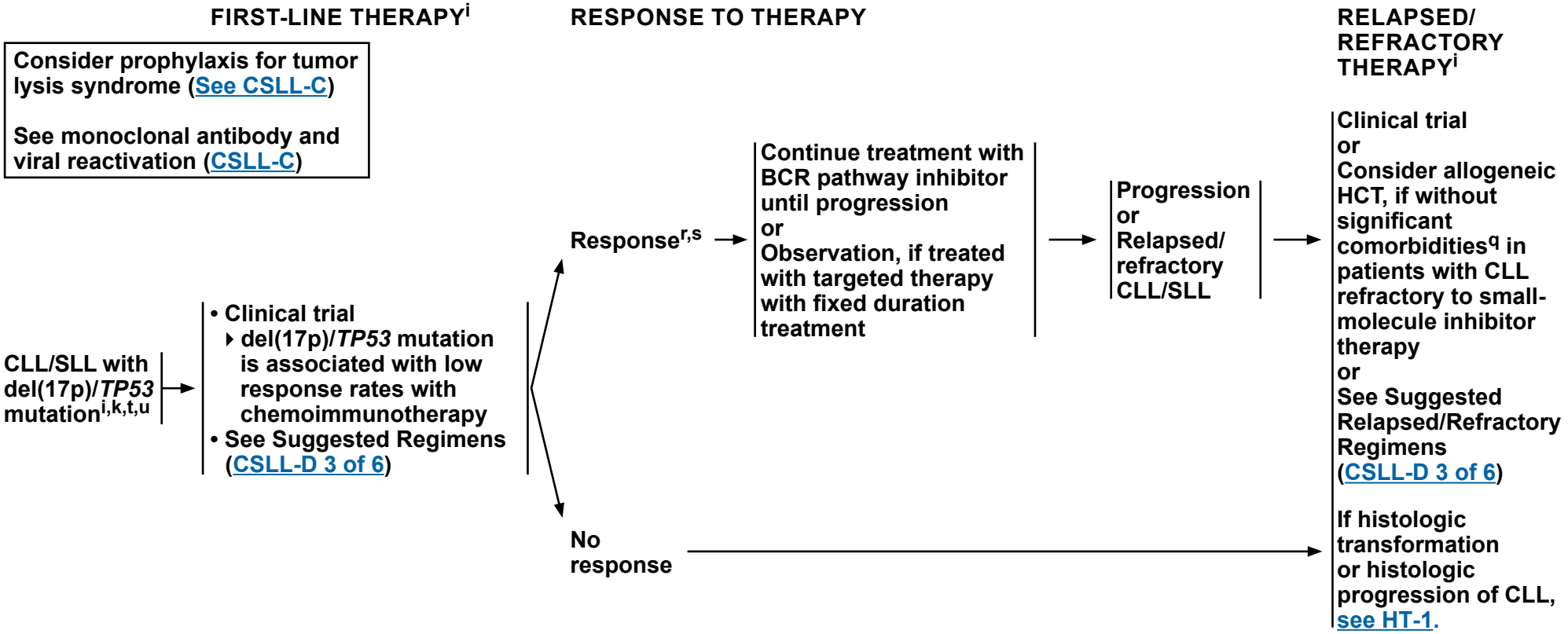
CLL/SLL WITH DELETION OF 17P/*TP53* MUTATION



[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

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

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

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

[d] Extent of disease is determined by PET/CT for avid lymphomas and CT for non-avid histologies.
[e] Categorization of A versus B has been removed from the Lugano Modification of Ann Arbor Staging System.
[f] Whether 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

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

SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Tumor Lysis Syndrome (TLS)

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

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

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

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

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

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Continued

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) • Acalabrutinib[f] ± obinutuzumab • 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) • Acalabrutinib[f] ± obinutuzumab • 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

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)

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

SUGGESTED TREATMENT REGIMENS[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 Footnotes on CSLL-D 4 of 6

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

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

Note: All recommendations are category 2A unless otherwise indicated.
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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**
• Acalabrutinib[f] ± obinutuzumab	• Alemtuzumab[p] ± rituximab
• Ibrutinib[f]	• HDMP + rituximab
• Venetoclax[f,g] + obinutuzumab	• Obinutuzumab

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

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)

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

SUGGESTED TREATMENT REGIMENS[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
REFERENCES

Acalabrutinib

Byrd J, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:323-332.

Ghia P, Pluta A, Wach M, et al. ASCEND phase 3 study of acalabrutinib vs investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) [abstract]. European Hematology Association Congress; 2019:Abstract LB2606.

Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Adv 2019;3:1553-1562.

Sharman JP, et al. ELEVATE TN: Phase 3 study of acalabrutinib combined with obinutuzumab (O) or alone Vs O plus Chlorambucil (Clb) in patients (Pts) with treatment-naive chronic lymphocytic leukemia (CLL) [abstract]. Blood 2019;134:Abstract 31.

Alemtuzumab

Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-5623.

Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: Results of a large international study. Blood 2002;99:3554-3561.

Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103:3278-3281.

Alemtuzumab + rituximab

Faderl S, Ferrajoli A, Wierda W, et al. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence. Cancer 2010;116:2360-2365.

BR (bendamustine + rituximab)

Michallet AS, Aktan M, Hiddemann W, et al. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica 2018;103:698-706.

Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2016;17:928-942.

Fischer K, Cramer P, Busch R et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-3566.

BR+ ibrutinib

Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. Leukemia 2019;33:969-980.

BR + idelalisib

Zelenetz AD, Barrientos JC, Brown JR, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2017;18:297-311.

Bendamustine + obinutuzumab

Stilgenbauer S, Leblond V, Foa R, et al. Obinutuzumab plus bendamustine in previously untreated patients with CLL: a subgroup analysis of the GREEN study. Leukemia 2018;32:1778-1786.

Bendamustine + ofatumumab

Flinn IW, Panayiotidis P, Afanasyev B, et al. A phase 2, multicenter study investigating ofatumumab and bendamustine combination in patients with untreated or relapsed CLL. Am J Hematol 2016;91:900-906.

Chlorambucil + obinutuzumab

Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Eng J Med 2014;370:1101-1110.

Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia 2015;29:1602-1604.

Duvelisib

Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood 2018;132:2446-2455.

Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients With Refractory Indolent Non-Hodgkin Lymphoma. J Clin Oncol 2019;37:912-922.

Davids MS, Kuss BJ, Hillmen P, et al. The Efficacy and Safety of Duvelisib Following Disease Progression on Ofatumumab in Patients with Relapsed/Refractory CLL or SLL: Updated Results from the DUO Crossover Extension Study [abstract] Blood 2018;132:Abstract 3140.

FCR (fludarabine, cyclophosphamide, rituximab)

Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. Blood 2016;127:208-215.

Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2016;17:928-942.

Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood 2016;127:303- 309.

Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756-1765.

Badoux XC, Keating MJ, Wang X, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood 2011;117:3016-3024.

FC (fludarabine, cyclophosphamide) + ofatumumab

Robak T, Warzocha K, Govind Babu K, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. Leuk Lymphoma 2017;58:1084-1093.

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

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

Continued

SUGGESTED TREATMENT REGIMENS
REFERENCES

Fludarabine + rituximab
Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.

HDMP (high-dose methylprenisolone) + rituximab
Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leukemia and Lymphoma 2007;48:2412-2417.
Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia 2009;23:1779-1789.
Thornton PD, Matutes E, Bosanquet AG, et al. High dose methylprednisolone can induce remissions in CLL patients with p53 abnormalities. Ann Hematol 2003;82:759-765.

Ibrutinib
Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia 2019:[Epub ahead of print].
Byrd JC, Brown JR, O'Brien S; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Eng J Med 2014;371:213-223.
O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol 2016;17:1409-1418.
Farooqui MZ, Valdez J, Martyr S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: A phase 2, single-arm trial. Lancet Oncol 2015;16:169-176.
Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol 2019: [Epub ahead of print].

Ibrutinib + rituximab
Shanafelt T, Wang X, Kay N, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med 2019;381:432-443.
Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med 2018;379:2517-2528.

Ibrutinib + obinutuzumab
Moreno C, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:43-56.

Idelalisib ± rituximab
Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. J Clin Oncol 2019;37:1391-1402.
Gopal A, Kahl B, De Vos S, et al. PI3Kd inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014; 370:1008-1018.

Lenalidomide
Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol 2006;24:5343-5349.
Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111:5291-5297.
Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2013;31:584-591.

Lenalidomide maintenance
Fink AM, Bahlo J, Robrecht S, et al. Lenalidomide maintenance after first-line therapy for high-risk chronic lymphocytic leukaemia (CLLM1): final results from a randomised, double-blind, phase 3 study. Lancet Haematol 2017;4:e475-e486.
Chanan-Khan AA, Zaritskey A, Egyed M, et al. Lenalidomide maintenance therapy in previously treated chronic lymphocytic leukaemia (CONTINUUM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol 2017;4:e534-e543.

Obinutuzumab
Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. Blood 2017;127:79-86.
Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood 2014;124:2196-2202.

Ofatumumab
Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-1755.
Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008;111:1094-1100.

Ofatumumab maintainance
van Oers MH, Kuliczkowski K, Smolej L, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. Lancet Oncol 2015;16:1370-1379.

PCR (pentostatin, cyclophosphamide, rituximab)
Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24:1575-1581.
Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 2007;109:405-411.

Venetoclax + obinutuzumab
Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med 2019;380:2225-2236.

Venetoclax ± rituximab
Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: Results from the full population of a phase II pivotal trial. J Clin Oncol 2018;36:1973-1980.
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.
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.
Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: Post-treatment follow-up of the MURANO phase III study. J Clin Oncol 2019;37:269-277.
Seymour JF1, Kipps TJ1, Eichhorst B1, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 2018;378:1107-1120.

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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.
[e] Kovacs G, Robrecht S, Fink AM, et al. Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic leukemia (CLL) who achieve partial response: Comprehensive analysis of rwo phase III studies of the German CLL Study Group. J Clin Oncol 2016;34:3758-3765.
[f] Thompson PA, Peterson CB, Strati P, et al. Serial minimal residual disease (MRD) monitoring during first-line FCR treatment for CLL may direct individualized therapeutic strategies. Leukemia 2018;32:2388-2398.
[g] Molica S, Giannarelli D, Montserrat E. Minimal residual disease and survival outcomes in patients with chronic lymphocytic leukemia: A systematic review and meta-analysis. Clin Lymphoma Myeloma Leuk 2019;19:423-430.
[h] Rawstron AC, Bottcher S, Letestu R, et al. Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual disease monitoring in CLL. Leukemia 2013;27:142-149.
[i] Rawstron AC, Fazi C, Agathangelidis A, et al. A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study. Leukemia 2016;30:929-936.
[j] Logan AC, Gao H, Wang C, et al. High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment. Proc Natl Acad Sci U S A 2011;108:21194-21199.
[k] Aw A, Kim HT, Fernandes SM, et al. Minimal residual disease detected by immunoglobulin sequencing predicts CLL relapse more effectively than flow cytometry. Leuk Lymphoma 2018;59:1986-1989.

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

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

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

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

Continued

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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.

Continued

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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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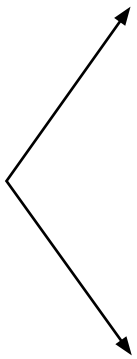
WORKUP

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

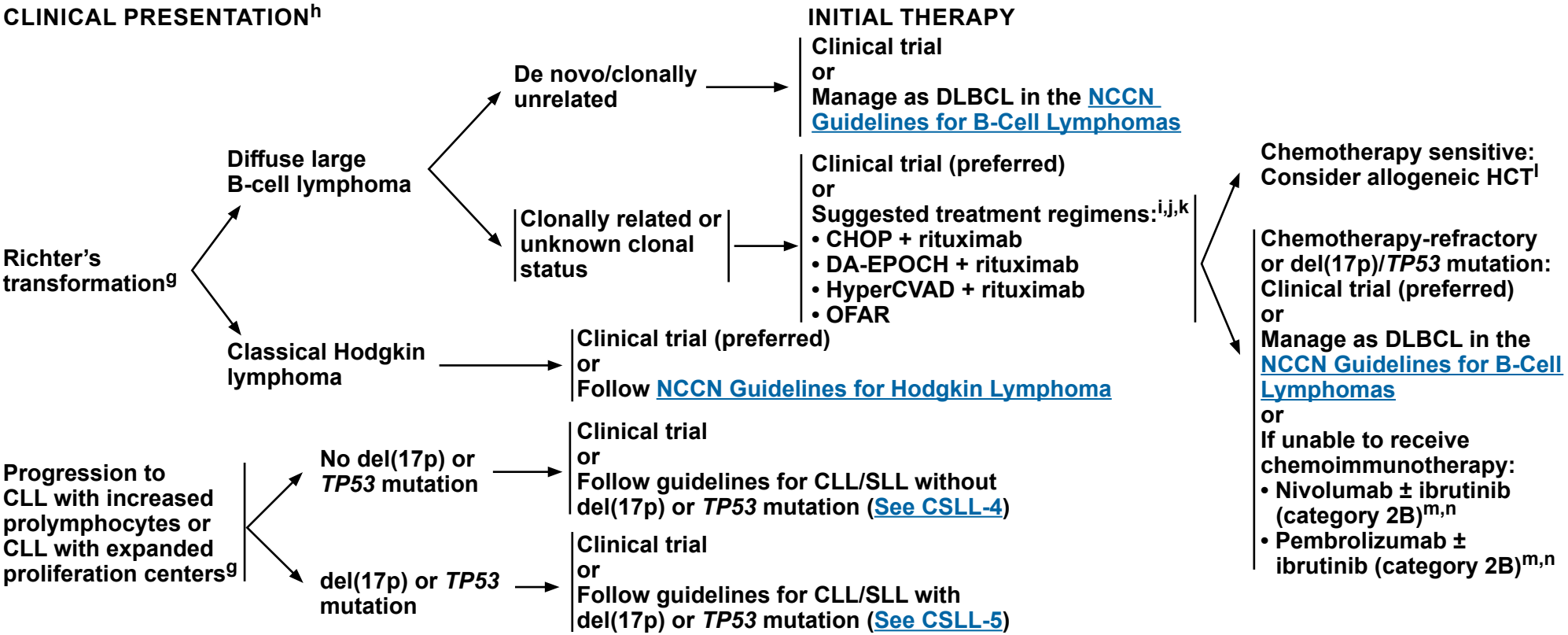


Richter's Transformation (HT-3)

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.

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



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

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

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

SUGGESTED TREATMENT REGIMENS
REFERENCES

DA-EPOCH-R

Rogers 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.

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

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

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.

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

Table of Contents

Overview

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are characterized by a progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. Morphologically, these leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or prolymphocytes. CLL remains the most prevalent adult leukemia in Western countries. In 2019, an estimated 20,720 people will be diagnosed with CLL in the United States, and an estimated 3930 people will die from the disease.[1] CLL and SLL are different manifestations of the same disease and are managed in much the same way.[2] The major difference is that in CLL, a significant number of the abnormal lymphocytes are found in the peripheral blood in addition to bone marrow and lymphoid tissue, while in SLL, the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues and there are few (if any) abnormal lymphocytes circulating in the peripheral blood.

Literature Search Criteria and Guidelines Update Methodology

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

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

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

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

Staging

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

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

The Binet staging system stratifies patients into 3 prognostic groups based on the number of involved areas and the level of hemoglobin and platelets and, similar to the Rai staging system, provides meaningful correlation with clinical outcome.[5]

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

Prognostic Factors

Immunoglobulin heavy chain variable region (*IGHV*) gene mutation 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]

Cytogenetic abnormalities detected by fluorescence in situ hybridization (FISH) are present in more than 80% of patients with previously untreated CLL. Del(13q) (55%), del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%) are the most common abnormalities at the time of diagnosis.[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] 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.[13,16,17]

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.[18] *TP53* abnormalities can occur in the absence of del(17p) and *TP53* mutations have been identified as predictors of resistance to fludarabine-based or bendamustine-based regimens and poor survival, independent of 17p chromosome status.[19-22]

The prognostic significance of *IGHV* mutation status and cytogenetic abnormalities has been evaluated in large prospective randomized studies evaluating chemotherapy or chemoimmunotherapy.[13,23,24] In the CLL4 trial (chlorambucil versus fludarabine versus fludarabine and cyclophosphamide [FC] as first-line therapy), the loss of *TP53* was found to be the strongest predictor of poor outcomes to first-line therapy.[13] In addition, del(11q) and treatment allocation were independent predictors for PFS and age was an independent predictor for OS. In the long-term follow-up from the CALGB 9712 study (concurrent versus sequential fludarabine and rituximab as first-line therapy), unmutated *IGHV* was a significant independent predictor for shorter PFS and OS, and del(17p) or del(11q) were independent predictors for shorter survival.[23] In the CLL8 (FC versus FCR as first-line therapy), the presence of *TP53* mutation, del(17p), and unmutated *IGHV* were the strongest predictors of shorter PFS and OS.[24]

Among the cell surface markers detected by flow cytometry, immunohistochemistry or methylation (CD38, CD49d, and ZAP-70), CD49d (≥30%) is the strongest predictor of OS and treatment-free survival.[25-29] CD38 expression (≥30%) [7,11,13,30-32] and/or ZAP-70 (≥20%) are associated with shorter PFS and OS outcomes.[33-38] In addition, it was suggested that ZAP-70 positivity may be a stronger predictor of clinical outcomes than *IGHV* mutation status or CD38.[36-38] ZAP-70 methylation (which is closely associated with ZAP-70 expression and *IGHV* mutation

status) was also reported to be a useful prognostic test for patients with CLL but is not routinely performed clinically.[39-41]

Beta-2 microglobulin is readily measured by standard laboratory evaluation of blood samples and an elevated level of serum beta-2 microglobulin was shown to be a strong independent prognostic indicator for treatment-free interval, response to treatment, and OS in patients treated with first-line chemoimmunotherapy.[42,43] However, it is influenced in a CLL disease-independent manner by renal dysfunction.

Recurrent mutations in *NOTCH1*, *SF3B1*, and *BIRC3* genes with prognostic implications have been identified in approximately 4% to 15% of patients with newly diagnosed CLL and the incidences are much higher (15%–25%) in patients with fludarabine-refractory CLL.[44-52] Several prognostic models incorporating traditional and newer prognostic markers have been developed for the risk stratification.[53-59]

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).[53] The estimated median survival times were not reached—10 years and 5 years—respectively, for the three risk groups. The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.[53] 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.[54,55]

In another prognostic model, increased size of cervical lymph nodes, three involved nodal sites, del(17p) or del(11q), unmutated *IGHV* status, and elevated serum LDH levels were identified as independent predictors of shorter time to first treatment.[56] This model may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention.

Integrated CLL Scoring System (ICSS) stratifies patients into three risk groups (low, intermediate, and high) based on the cytogenetic abnormalities detected by FISH, *IGHV* mutation status, and CD38 expression.[58] International prognostic index for CLL (CLL-IPI) stratifies patients into four risk groups (low, intermediate, high, and very high) based on *TP53* and *IGHV* mutation status, serum beta-2 microglobulin concentration, clinical stage, and age.[59] The 5-year OS rates were significantly different between these risk groups (93%, 79%, 63%, and 23%, respectively). CLL-IPI has been validated in an independent cohort of patients with newly diagnosed CLL and is also useful for predicting time-to-first treatment and risk of progression in patients receiving first-line chemoimmunotherapy.[60,61]

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

Early progression of disease (POD) within 2 years of first-line therapy has been identified as a prognostic factor for inferior clinical outcomes in patients with CLL.[62] In an analysis of 829 patients, early POD after first-line treatment was associated with unfavorable cytogenetics (del 11q or del 17p) and inferior ORR to first-line treatment. The ORR was 53% for those with early POD compared to 80% and 84%, respectively, for those with late POD and no POD. Early POD was also associated with inferior

OS across all patients and in patients treated with chemoimmunotherapy (FCR or bendamustine + rituximab [BR]; $P < .05$).

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

Complex karyotype (CK; ≥3 unrelated chromosomal abnormalities in more than one cell on CpG-stimulated karyotype of CLL cells) may be a stronger predictor of poor clinical outcomes than del(17p) or *TP53* mutation in patients with CLL treated with ibrutinib-based regimens.[63-68] In a multivariate analysis, among patients with relapsed/refractory CLL treated with ibrutinib-based regimens, only CK was significantly associated with inferior event-free survival (EFS; $P = .006$), whereas CK ($P = .008$) and fludarabine-refractory CLL ($P = .005$) were independently associated with inferior OS.[64] In another analysis of 308 patients treated with ibrutinib on four sequential clinical trials, in a multivariate analysis, CK at baseline, presence of del(17p), and age <65 years were all independently associated with a risk for CLL progression.[69] In patients ≥65 years without CK or del(17p), the estimated cumulative incidence of CLL progression at 4 years was 2% compared to 44% in patients <65 years with CK and del(17p). A more recent retrospective analysis of >5,000 patients with available cytogenetic data suggests that CK is associated with variable clinical behavior.[68] High CK (≥5 unrelated chromosomal abnormalities) emerged as an adverse prognostic factor independent of clinical stage, *IGHV* mutation status, and *TP53* aberrations (del(17p) and/or *TP53* mutation) whereas low CK (three unrelated chromosomal abnormalities) and intermediate CK (four unrelated chromosomal abnormalities) were clinically relevant only if coexisting with *TP53* aberrations.

Acquired resistance to ibrutinib is predominantly mediated by *BTK* and *PLCG2* mutations which have been detected in patients with relapsed CLL after treatment with ibrutinib at an estimated median of 9 months before relapse.[69,70] *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.[71] Similar mutations have also been described in patients receiving acalabrutinib.[72] These findings suggest that testing for these mutations may be helpful to confirm resistance to ibrutinib or acalabrutinib. However, the reported variant allele frequencies (VAF) are variable with often low VAF associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance.[69,71] Testing for mutations as screening for resistance is not currently recommended.

Response Criteria

The response criteria developed by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) are outlined in CSLL-E. In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. The IWCLL guidelines provide further recommendations for the evaluations and response assessments appropriate for the general clinical practice setting versus for clinical trials.[73]

Immunomodulating agents such as lenalidomide can result in a tumor flare reaction characterized by painful enlargement of lymph nodes, lymphocytosis, rash, and bone pain. Tumor flare reaction correlated with clinical response in patients with CLL treated with lenalidomide.[74]

B-cell receptor (BCR) pathway inhibitor (BCRi) therapy with Bruton's tyrosine kinase inhibitors (BTKi; ibrutinib and acalabrutinib) and phosphatidylinositol 3-kinase inhibitors (PI3Ki; idelalisib and duvelisib) cause early mobilization of lymphocytes into the blood resulting in a transient lymphocytosis in most patients, which does not signify disease progression.[75-77] Prolonged lymphocytosis following ibrutinib treatment was reported to represent the persistence of a quiescent clone and slow or incomplete resolution of lymphocytosis does not appear to impact outcome as measured by PFS.[75]

Considering these findings, the IWCLL response criteria were revised to more precisely predict the outcome of patients with CLL treated with immunomodulating agents and BCRi.[78] The revised IWCLL response criteria allow for a new response category, "PR with lymphocytosis," for patients receiving BTKi (ibrutinib or acalabrutinib) or PI3Ki (idelalisib or duvelisib) to include clinical response (reduction in lymph nodes and splenomegaly) with persistent lymphocytosis (in the absence of other indicators of progressive disease). Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

Undetectable minimal residual disease (MRD; $<10^{-4}$ detectable leukemic cells in peripheral blood or bone marrow) after the end of treatment (EOT) is associated with long-term survival.[79-82] 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 partial response (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).[79] The persistence of post-treatment splenomegaly as a sole abnormality in MRD-negative patients did not have a negative impact on PFS. In a prospective study of 289 patients with CLL, undetectable MRD at end of first-line chemoimmunotherapy with FCR correlated with longer PFS.[80] The median PFS was not reached for patients with undetectable MRD 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 by the EOT (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%. The prognostic significance of MRD after EOT with venetoclax + obinutuzumab was confirmed in the prospective analysis of the CLL14 study.[82] In this study, venetoclax + obinutuzumab achieved higher rates of undetectable MRD at EOT than chlorambucil + obinutuzumab both in the peripheral blood (76% vs. 35%) and bone marrow (57% vs. 17%). The 24-month PFS rate for venetoclax + obinutuzumab was higher for patients with undetectable MRD compared to those with detectable MRD (89% vs. 62%) and the undetectable MRD translated into improved PFS regardless of the clinical response status at EOT.

These findings suggest that undetectable MRD in the peripheral blood after the end of treatment is an important predictor of treatment efficacy, supporting the integration of MRD assessment as part of response evaluation. Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and six-color flow cytometry (MRD flow) are the two validated methods used for the detection of MRD at the level of 10^{-4} to 10^{-5}.[83,84] Next-generation DNA sequencing (NGS)-based assays have been reported to be more sensitive allowing for the detection of MRD at the level of 10^{-6}.[84-86]

Diagnosis

The diagnosis of CLL requires the presence of at least 5×10^9/L monoclonal B-lymphocytes in the peripheral blood and the clonality of B cells should be confirmed by flow cytometry.[73] 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.[73] B-cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when effacement of the lymph node architecture is observed in biopsy samples.

Flow cytometry of peripheral blood with immunophenotyping using cell surface markers is adequate for the diagnosis of CLL, and bone marrow biopsy is generally not required. A diagnosis of SLL should ideally be confirmed by lymph node biopsy. Evaluation of cyclin D1 (flow cytometry or IHC) or FISH analysis for t(11;14), flow cytometry evaluation of CD200, and IHC for LEF1 may be helpful in the differential diagnosis of CLL, especially to exclude other CD5+ B-cell lymphoproliferative disorders specifically mantle cell lymphoma.[87-90]

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

Interphase FISH is the standard method to detect specific chromosomal abnormalities that may have prognostic significance. Conventional metaphase FISH is difficult in CLL due to the very low *in vitro* proliferative activity of the leukemic cells. CpG oligonucleotide stimulation can be utilized to enhance metaphase cytogenetics.[91,92]

Molecular analysis for *IGHV* mutation status is preferred over flow cytometry. *IGHV* mutation testing is recommended based on reproducibility and ready availability. A variety of *IGHV*% cut-off levels ranging from 1% to 5% have been studied.[93] In a retrospective analysis of 203 patients treated with the FCR (fludarabine, cyclophosphamide, and rituximab) regimen, higher *IGHV*% levels were incrementally associated with favorable progression-free survival (PFS) and overall survival (OS), suggesting that *IGHV*% is a continuous variable in patients treated with the FCR regimen.[94] A cut-off level of ≤2% *IGHV* mutation is routinely used in clinical practice to differentiate patients with *IGHV*-mutated CLL from those with *IGHV*-unmutated CLL.[95,96] Patients with *IGHV* mutated CLL by this definition can have long-term progression free survival following FCR (54% at 13 years).[97] *IGHV* mutation status is necessary when considering treatment with chemoimmunotherapy.

CD38, CD49d, and ZAP-70 expression correlate with unmutated *IGHV*, and these have been proposed as surrogate markers for *IGHV* mutation status.[7,26,33,34] However, discordant results between *IGHV* mutation status and CD38 or ZAP-70 positivity have been reported in about 20% to 28% of cases.[13,36,98] Furthermore, standardization and reproducibility of these markers across laboratories remains a challenge. Evaluation of CD38, CD49d, and ZAP-70 is not recommended outside the context of clinical trials.

Monoclonal B-cell lymphocytosis

MBL is a condition in which an abnormal B-cell population with immunophenotype of CLL or related low grade lymphoproliferative disorder but do not meet the diagnostic criteria for CLL.[99,100] An absolute monoclonal B-lymphocyte count of <5 x 10^9/L that is stable over a 3-month period in the absence of palpable lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder (anemia, thrombocytopenia, constitutional symptoms, organomegaly) is defined as monoclonal B-cell lymphocytosis (MBL).[101]

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.[102,103] 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.[104] 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.[105]

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.[100] 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.[53] Reticulocyte counts and a direct Coombs test should be performed to evaluate for the possibility of hemolysis and pure red cell aplasia (PRCA) in patients with anemia.

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

CT scans may be useful for the evaluation of symptoms or bulky disease, to monitor disease progression in patients with new symptoms when peripheral adenopathy is not present or for the assessment of tumor lysis syndrome (TLS) risk category prior to the initiation of venetoclax. However, serial CT scans are not recommended for asymptomatic patients. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.[106,107]

Biosimilars

A biosimilar is a biological product that is highly similar to the FDA-approved reference biological product with the exception of minor differences in clinically inactive components and no clinically meaningful differences in safety, purity, or potency.[108]

Pharmacokinetic (drug exposure) and pharmacodynamic (response) studies in the appropriate patient population are essential to demonstrate the efficacy and safety of the biosimilar.[109] Biosimilars require only one clinical trial to demonstrate equivalent safety and efficacy in the most sensitive indication for the reference biological product. If the mechanism of action, pharmacokinetics, and pharmacodynamics are similar, the biosimilar may be approved for all of the same indications as the reference biological product and can be substituted for the reference biological product.[109]

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

Alternating between the biosimilar and the reference product is acceptable without the intervention of a health care provider only if a biosimilar is designated as interchangeable since such a substitution will not result in higher toxicity or diminished efficacy.[108] However, alternating

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

Rituximab-abbs and rituximab-pvvr are the two FDA-approved biosimilars for use in combination with FC in patients with CLL. The approval is based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic data, clinical immunogenicity data, and other clinical data that demonstrate rituximab-abbs and rituximab-pvvr are biosimilar to rituximab in terms of safety and efficacy.[110-112] These two biosimilars have not been approved as interchangeable biological products. Therefore, during a single course of therapy, the patient should remain on the same product that was used to initiate treatment throughout the course of the treatment.

Localized SLL (Lugano stage I)

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

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

Early-stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. In the absence of disease symptoms, a “watch and wait” approach is often appropriate for patients with stage II–IV SLL, low-risk CLL (Rai stage 0 or Binet A), or intermediate-risk CLL (Rai stage I–II or Binet B) and treatment will be beneficial if they become symptomatic or show evidence of progressive disease.[73] 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; or steroid-refractory autoimmune cytopenia.[73] Absolute lymphocyte count alone is not an indication for treatment and symptoms related to leukostasis are exceedingly rare in CLL patients.[73]

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

Assessment of Functional Status and Comorbidity

CLL/SLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. The age cutoff of 65 years is used in most of the clinical trials, including the studies conducted by the GCLLSG.[113] Comorbidities are frequently present in older patients and the presence of multiple comorbidities (≥2 comorbidities) was an independent predictor of clinical outcome, independent of patients’ age or disease stage.[114] 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.[114,115] In the CLL14 study, CIRS score >6 or an estimated CrCl <70 mL/min was used as the eligibility criteria for patients with significant comorbidities.[116]

Patients are stratified into 3 groups based on their functional status and presence or absence of comorbidities: frail patients with significant comorbidities, patients ≥65 years or younger patients with significant comorbidities (CrCl <70 mL/min), and patients <65 years without significant comorbidities.

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.

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 randomized trials, first demonstrated in the RESONATE-2 study[117,118] and more recently in the Alliance North American Intergroup Study (A041202).[22]

In the RESONATE-2 study, 269 patients (≥65 years of age) were randomized to receive ibrutinib (420 mg continuous treatment) or chlorambucil as first-line therapy.[117] After a median follow-up of 5 years, ibrutinib resulted in significantly higher overall response rate (ORR; 92% vs. 37%; *P* < .0001) and significantly longer PFS rate (70% vs. 12% at 60 months; *P* < .0001) compared to chlorambucil.[118] With 57% of patients switching to ibrutinib after disease progression on chlorambucil, the estimated 5-year OS rates (without censoring for crossover from chlorambucil to ibrutinib) were 83% and 68% respectively, for patients treated with ibrutinib and chlorambucil. Neutropenia (13%), pneumonia (12%), hypertension (8%) and anemia (7%) were the common grade ≥3 adverse events. Ibrutinib also improved PFS compared to chlorambucil in patients with high risk CLL and the estimated 5-year PFS rates were 79% and 67% respectively for patients with del(11q) and unmutated *IGHV.*

In the Alliance North American Intergroup Study (ibrutinib monotherapy [n = 182] versus ibrutinib + rituximab [n = 182] versus BR [n = 183]), ibrutinib monotherapy and ibrutinib + rituximab resulted in superior ORR and PFS compared to BR in patients ≥65 years with untreated CLL.[22] 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). There was no difference in PFS between treatment groups based on *IGHV* mutation status. The 2-year OS rates, however, were not significantly different among the treatment arms (90%, 94%, and 95%, respectively, for the three treatment arms; *P* =. 87). The presence of CK did not have an impact on PFS among patients treated with ibrutinib. The estimated 2-year PFS rates were 91% and 87%, respectively for ibrutinib and ibrutinib + rituximab among patients with CK. This study also showed primary benefit for ibrutinib and ibrutinib + rituximab in patients with unmutated *IGHV* (61% of patients had unmutated *IGHV*) rather than mutated *IGHV.*

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 in patients ≥65 years without del(17p). The panel consensus was to continue the listing of ibrutinib with a category 1 recommendation for frail patients with significant comorbidities (not able to tolerate purine analogs) and for patients ≥65 years or younger patients with significant comorbidities.

The ECOG-ACRIN cancer research group (E1912) study showed that ibrutinib + rituximab was more effective than FCR for patients ≤70 years without del(17p)/*TP53* mutation, especially in patients with unmutated *IGHV*.[119] These results suggest that ibrutinib may be an appropriate option (instead of chemoimmunotherapy) for younger patients with *IGHV* unmutated CLL who do want to enroll in a clinical trial. Therefore, based on the results of the E1912 study, the panel consensus was to change the recommendation of ibrutinib from a category 2A to category 1 recommendation for patients <65 years without del(17p) or *TP53* mutation.

Acalabrutinib ± obinutuzumab

The ELEVATE-TN phase III study randomized 535 patients (≥65 years or <65 years with coexisting conditions [CIRS score >6, CrCl <70 mL/min) to acalabrutinib + obinutuzumab (n=179), acalabrutinib (n= 179), or chlorambucil + obinutuzumab (n=177).[120] Acalabrutinib was given continuously until disease progression and obinutuzumab was added to acalabrutinib and chlorambucil for 6 cycles. The ORRs were higher with acalabrutinib + obinutuzumab (94%; 13% CR) and acalabrutinib monotherapy (85% consisting entirely PRs) than chlorambucil + obinutuzumab (79%; 5% CR). At a median follow-up of 28 months, acalabrutinib ± obinutuzumab significantly improved PFS compared to chlorambucil + obinutuzumab (*P* <.0001). The estimated 2-year PFS rates were 93%, 87%, and 47% for acalabrutinib + obinutuzumab, acalabrutinib, and chlorambucil + obinutuzumab, respectively. Acalabrutinib + obinutuzumab was associated with a PFS benefit in patients with *IGHV* unmutated CLL as well as *IGHV* mutated CLL compared to chlorambucil + obinutuzumab. This study, however, was not powered to compare the PFS benefit between the two acalabrutinib arms. The estimated 2-year OS rates were 95%, 95%, and 92%, respectively. There was a trend towards improved OS for acalabrutinib ± obinutuzumab, despite cross over for disease progression in the chlorambucil + obinutuzumab arm, though longer follow-up is needed to confirm any OS benefit. The incidences of grade ≥3 neutropenia were higher with chlorambucil + obinutuzumab (70%) than with acalabrutinib + obinutuzumab (30%) and the addition of obinutuzumab increased neutropenia compared to acalabrutinib (10%).

Acalabrutinib was recently granted broad FDA approval for the treatment of patients with untreated and relapsed/refractory CLL. Based on the results of the ELEVATE-TN trial, the panel consensus was to include acalabrutinib ± obinutuzumab with a category 2A recommendation for all patients with CLL without del(17p) or *TP53* mutation.

Venetoclax + Obinutuzumab

The CLL14 study evaluated venetoclax + obinutuzumab versus chlorambucil + obinutuzumab for previously untreated CLL in 432 patients with comorbidities (CIRS score >6 and/or an estimated CrCl <70 mL/min; 216 patients in each treatment group).[116] Fixed-duration treatment with 12 cycles of venetoclax 400 mg daily or chlorambucil was given and both groups received obinutuzumab for first 6 cycles. After a median follow-up of 29 months, the ORR (85% vs. 71%; *P* < .001), CR rate (50% vs. 23%), and 24-month PFS rate (88% vs. 64%; HR, 0.35; *P* < .001) were significantly higher for venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab. There was no difference in PFS between treatment groups for patients with mutated *IGHV*. The median OS was not reached in either treatment group. The undetectable-MRD rate ($<10^{-4}$ as assessed by ASO-PCR assay) at 3 months after 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). 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. Grade 3 or 4 neutropenia occurred in 53% of patients in the venetoclax + obinutuzumab group and in 48% of patients in the chlorambucil + obinutuzumab group. Grade 3 or 4 infections occurred in 18% and 15% of patients, respectively.

Venetoclax in combination with obinutuzumab 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 comorbidities (not able to tolerate purine analogs) and patients ≥65 years or younger patients with significant comorbidities based on the results of the CLL14 study.[116]

The CLL14 study established the efficacy of this combination only in patients with comorbidities (CIRS score >6 or an estimated CrCl <70 mL/min).[116] The panel members acknowledged that the efficacy of this combination in patients without significant comorbidities has not been established in a randomized clinical trial. However, with the recent FDA approval, some panel members agreed that venetoclax + obinutuzumab may be an appropriate fixed-duration chemotherapy-free treatment option for younger patients without comorbidities who do want to enroll in a clinical trial. Therefore, initially, the consensus of the panel was to include venetoclax + obinutuzumab as an option under “other recommended regimens” with a category 2B recommendation for patients <65 years of age without significant comorbidities. After re-review of the data from the CLL14 study (following the publication of the full paper), the panel consensus was to change the recommendation of venetoclax + obinutuzumab from category 2B (other recommended regimen) to category 2A (preferred regimen) for patients <65 years of age without significant comorbidities.

First-Line Therapy: Other Recommended Regimens

Bendamustine + Anti-CD20 Monoclonal Antibody

Bendamustine + anti CD20 mAb (obinutuzumab, ofatumumab or rituximab) has demonstrated activity in patients with previously untreated CLL resulting in an ORR of 81% (35% CR) to 95% (43% CR).[121-123]

In the CLL10 study (discussed below), there was no significant difference in PFS between BR and FCR as first line therapy for CLL without del(17p), in patients >65 years, although the PFS benefit of FCR was significant in physically fit patients <65 years.[124] The incidence of severe neutropenia and infections was significantly more frequent in the FCR arm, especially among patients >65 years. The updated results of the CLL10 study also confirmed that BR is associated with a decreased risk of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).[124] After a median follow-up of 58 months, the incidences of secondary AML and MDS were 3% and 1% in FCR and BR arms, respectively.

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

Chlorambucil + Obinutuzumab

CLL11 study established that chlorambucil + obinutuzumab is superior to chlorambucil + rituximab for elderly patients and for those with comorbidities lacking del(17p) or *TP53* mutation.[125]

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).[126] Ibrutinib was given continuously until disease progression and both groups received obinutuzumab for first 6 cycles. 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%).

Based on the results of the iLLUMINATE study, the panel consensus was to change the recommendation of chlorambucil + obinutuzumab from category 1 (preferred regimen) to category 2A (other recommended regimen) for frail patients with significant comorbidities and patients ≥65 years or younger patients with significant comorbidities. Chlorambucil + rituximab or ofatumumab is no longer recommended as an option for first-line therapy for this group of patients based on the results of the CLL11 study that established the superiority of chlorambucil + obinutuzumab over chlorambucil + rituximab for elderly patients and for those with comorbidities.

Fludarabine, Cyclophosphamide, and Rituximab

The 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*.[24,97,124]

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.[24] 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).[97] 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).[124] The median age was 62 years, but a significantly higher proportion of patients were >65 years in the BR arm (39% vs. 30%). After a median follow-up of 37 months**,** the ORR was 95% for FCR and 96% for BR (*P* = 1.0) with no difference in OS (3-year OS rate was 91% for FCR vs. 92% for BR; *P* = .89). FCR resulted in higher CR rate (40% vs. 31%), more MRD negativity (59% vs. 26% at 12 months; *P* < .0001; 55% vs. 27% at 18 months; *P* = .002), and longer median PFS (55 months vs. 42 months; *P* = .0003) compared to BR. The PFS benefit of FCR was significant in physically fit patients <65 years and in patients with mutated *IGHV*. The median PFS was 54 months and 39 months, respectively, for FCR and BR in patients ≤65 years (*P* = .0004) and there was no significant difference in PFS between the treatment groups for patients >65 years (median not reached for FCR and 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 [ibrutinib was given continuously until disease progression and rituximab was added for the first 6 cycles] and 175 patients were randomized to 6 cycles of FCR).[119] At median follow-up of 34 months, ibrutinib + rituximab was associated with significantly improved PFS (89% vs. 73% at 3 years; HR, 0.35; *P* < .0001) and OS (99% vs. 92% at 3 years; HR, 0.17; *P* < .0001) compared to FCR. In a subgroup analysis for PFS, ibrutinib + rituximab was more effective than FCR, especially for patients with unmutated *IGHV* (91% vs. 63% at 3 years; HR, 0.26; *P* < .0001), but ibrutinib + rituximab was not superior to FCR in patients with mutated *IGHV* (87.7% vs. 88%; HR, 0.44; *P* = .07). The extended follow-up results also confirmed these findings.[127] The incidences of grade ≥3 neutropenia [45% vs. 26%], and neutropenic fever (20% vs. 11%) were higher with FCR, whereas the incidences of grade ≥3 cardiac toxic effects (7% vs. 2%), atrial fibrillation (7% vs. 3%), hypertension (19% vs. 8%), and hemorrhagic events (grade ≥3; 1% vs 0%) 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 is the preferred first-line therapy option for *IGHV*-mutated CLL in patients <65 years without significant comorbidities.

An oral formulation of fludarabine is approved by the FDA for the treatment of patients with CLL that has not responded to or has progressed during or after treatment with at least one standard alkylating-agent containing regimen.[128-130] However, the efficacy and safety of the oral formulation compared with IV fludarabine has not been established in prospective randomized trials. Therefore, the NCCN Guidelines cannot recommend the appropriate use of oral fludarabine at this time.

Fludarabine + Rituximab

Fludarabine with concurrent or sequential administration of rituximab was evaluated in the CALGB 9712 study in patients with untreated CLL.[23,131] 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).[131] 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%.[23]

Fludarabine + rituximab (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 + Rituximab

High-dose methylprednisolone (HDMP) + rituximab is included with a category 2B recommendation for all patients, regardless of patient's age and comorbidities.[132] HDMP + rituximab was associated with a lower risk of myelosuppression and lower incidences of infectious complications (attributed to treatment in the frontline setting, good performance status of the patients, use of anti-infective prophylaxis during treatment, and the administration of intravenous immunoglobulin [IVIG] to patients with infections and hypogammaglobulinemia).

Ibrutinib + rituximab or obinutuzumab

The results of recent randomized phase III trials demonstrated that ibrutinib + rituximab is more effective than chemoimmunotherapy with BR (Alliance North American Intergroup Study)[27] and ibrutinib + obinutuzumab is more effective than chlorambucil + obinutuzumab (iLLUMINATE study)[22,126] for untreated CLL without del(17p) or *TP53* mutation in patients ≥65 years and for patients <65 years with comorbidities. Ibrutinib + obinutuzumab was recently approved by the FDA for first-line therapy based on the results of the iLLUMINATE study.[126] 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*.[119,127]

However, the results of 2 randomized studies did not show a benefit for the addition of rituximab to ibrutinib.[22,133] In the Alliance North American Intergroup Study (A041202), the estimated 2-year PFS rates were 88% and 87%, respectively, for ibrutinib + rituximab and ibrutinib monotherapy (P = .49).[22] In a single center randomized study of 208 patients with high-risk CLL (27 patients with untreated CLL), at a median follow-up of 36 months, the estimated PFS rates were 86% and 87% respectively, for ibrutinib and ibrutinib + rituximab.[133]

The majority of the panel members acknowledged that the addition of rituximab to ibrutinib has not yet demonstrated improvement in clinical outcomes compared to ibrutinib monotherapy in a randomized clinical trial and there are no randomized clinical trials that have compared ibrutinib and ibrutinib + obinutuzumab. In all of the above mentioned randomized clinical trials that have evaluated ibrutinib + rituximab or obinutuzumab, ibrutinib was given continuously until disease progression and obinutuzumab or rituximab was added to the combination arm only for the first 6 cycles. Therefore, the consensus was that the longer PFS was more the result of continuous and indefinite treatment with ibrutinib, rather than due to the contribution of an anti-CD20 mAb (rituximab or obinutuzumab) during the first 6 months of treatment. Improved outcomes with addition of an anti-CD20 mAb may more likely be seen with fixed-duration treatment with this regimen.

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

Pentostatin, Cyclophosphamide, and Rituximab

Pentostatin, cyclophosphamide, and rituximab (PCR) regimen is included as an option with a category 3 recommendation for patients <65 years

without significant comorbidities.[134-136] In a phase III randomized trial that compared PCR and FCR regimens in 184 patients with previously untreated (80% of patients) or minimally pretreated CLL, although the ORRs were similar for PCR and FCR (49% vs. 59%), the CR rate was lower in the PCR group (7% vs.14%; *P* = .04).[136] The incidence of grade 3 or 4 infectious events and neutropenia were similar between treatment arms, with increased incidence of leukopenia and thrombocytopenia in the FCR group.[136]

Monotherapy with Rituximab, Obinutuzumab or Chlorambucil

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

Obinutuzumab monotherapy is included with a category 2B recommendation and monotherapy with rituximab or chlorambucil is included with a category 3 recommendation for frail patients with significant comorbidities and for patients ≥65 years or younger patients with significant comorbidities.[137,138,139]

Post First-line Maintenance Therapy

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

Lenalidomide maintenance after first-line chemoimmunotherapy is included as an option under *Other Recommended Regimens* for CLL without del(17p)/*TP53* mutation in high-risk patients (MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated *IGHV*) based on the results of the CLLM1 study.[140]

Relapsed or Refractory Therapy: Preferred Regimens

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

Acalabrutinib, ibrutinib, and VenR are included with a category 1 recommendation, based on the results of the phase III randomized studies (ASCEND, RESONATE and MURANO, respectively).[141-143] Although the panel acknowledged that duvelisib and IdR are preferred treatment options based on the efficacy data (in terms of median PFS) from randomized phase III studies,[144,145] the panel consensus was to include duvelisib and IdR with a category 2A recommendation due to their toxicity profile (colitis, diarrhea, and increased risk of infections).

Acalabrutinib

In a phase II study of 134 patients with relapsed or refractory CLL, acalabrutinib resulted in an ORR of 94% (4% CR; 84% PR; 6% PR with lymphocytosis and the ORRs were consistently high across all high-risk subgroups including those with del (11q) or unmutated *IGHV* (95% for both subgroups).[77,146] After a median follow-up of 42 months, the estimated median PFS was not reached, and the PFS rate was 68%.[146]

The ASCEND trial (310 patients were randomized to receive acalabrutinib or the investigator's choice of IdR or BR) confirmed that acalabrutinib is superior to IdR or BR in terms of prolonging PFS in patients with relapsed/refractory CLL.[143] The ORR was 81% and 76% for acalabrutinib and IdR or BR, respectively. After a follow-up of 16 months, the median PFS was not reached, 16 months, and 17 months for acalabrutinib, IdR, or BR respectively ($P < .0001$). The 1-year PFS rates were 88%, 68%, and 69%, respectively. The median OS was not different between the treatment groups. At the time of this interm analysis, 51% of patients randomized to IdR or BR with documented disease progression had crossed over to acalabrutinib. Headache (22%), neutropenia (19%), diarrhea (18%), anemia (15), cough (15%), pyrexia (12%), fatigue (10%), and nausea (7%) were the most common adverse events of any grade observed in ≥15% of patients treated with acalabrutinib.

Patients with ibrutinib intolerance have also been successfully treated with acalabrutinib without recurrence of symptoms.[147] In a cohort of 33 patients with ibrutinib intolerance, after a median follow-up of 19 months, the ORR (including PR with lymphocytosis) was 76% and the median PFS was not reached. The estimated 1-year and 2-year PFS rates were 83% and 75%, respectively. Diarrhea (58%), headache (39%), cough (33%), weight increase (30%), nausea (27%), upper respiratory tract infection (24%), arthralgia (21%), pyrexia (21%), and fatigue (18%) were the most common adverse events of any grade observed in ≥20% of patients. Grade 3 or 4 neutropenia (12%) and thrombocytopenia (9%) were the most common grade 3 or 4 adverse events.

Acalabrutinib is recommended for relapsed/refractory therapy, regardless of patient's age and comorbidities. Based on the results of the ASCEND trial, the panel consensus was to change the recommendation of acalabrutinib from category 2A (other recommended regimen) to category 1 (preferred regimen).[143] Acalabrutinib is not effective for ibrutinib-refractory CLL with *BTK C481S* mutations.

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).[141] The final analysis of this study (up to 6-year follow-up) 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.[148] At a median follow-up of 74 months, the median PFS (44 months vs. 8 months for ofatumumab; $P < .0001$) and the estimated 5-year PFS rate (40% vs. 3%) were significantly better for ibrutinib. At the time of this analysis, 68% of patients randomized to ofatumumab had crossed over to ibrutinib. The ORR was 91% and the median OS (with censoring or adjustment for patients who have crossed over to ibrutinib) was better for ibrutinib ((HR, 0.64). Grade ≥3 atrial fibrillation and hypertension occurred in 9% and 6% of patients, respectively. The incidence of most of the grade ≥3 adverse events (neutropenia, pneumonia, and atrial fibrillation) decreased with follow-up.

Venetoclax + Rituximab

The results of a phase III randomized study (MURANO) demonstrated that fixed duration of treatment with VenR is associated with superior outcomes compared to BR in patients with relapsed/refractory CLL.[142] In this study, 389 patients were randomized to receive 6 cycles of VenR (n = 194) or BR (n = 195). Patients received venetoclax monotherapy for 2 years after completing 6 cycles of VenR. After a median follow-up of 24 months, the 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. Post-treatment follow-up at 36 months confirmed the superiority of VenR over BR in terms of undetectable MRD, PFS, and OS rates.[149] The undetectable MRD after completion of treatment with VenR was a predictor of longer PFS (low-level MRD [10^{-4} to $<10^{-2}$] was associated with improved PFS compared with high-level MRD [$\geq 10^{-2}$]).

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.[144,150,151]

In the DUO study, 319 patients with relapsed/refractory CLL/SLL were randomized to either duvelisib (n = 160) or ofatumumab (n = 159).[144] Patients who had received prior treatment with BTKi or PI3Ki 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).[150] 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 non-Hodgkin's lymphomas (NHL) (28 patients with relapsed/refractory SLL), duvelisib resulted in an ORR of 47% (68% for patients with SLL).[151] 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.

Idelalisib + Rituximab

In the multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with either idelalisib (150 mg) or placebo.[145] 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 IdR. At 24 weeks, the PFS rate was 93% and 46% in the idelalisib group and placebo group, respectively.[145] After a median follow-up of 18 months, IdR significantly improved ORR (84% vs. 16%; *P* < .001), median PFS (19 months vs. 6 months), and median OS (41 months vs. 35 months), compared to rituximab + placebo in patients with relapsed CLL with coexisting conditions.[152] Pyrexia (40%), diarrhea (29%), and rash (25%) were the most common adverse events in the idelalisib group.

IdR is an appropriate treatment option for relapsed/refractory CLL/SLL in patients for whom rituximab monotherapy would be considered

appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or grade ≥3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).

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

Relapsed/Refractory Therapy: Other Recommended Regimens

Alemtuzumab ± Rituximab

Alemtuzumab (subcutaneous or intravenous) ± rituximab has demonstrated activity in patients with fludarabine-refractory CLL and is included as an option, regardless of patient's age or comorbidities.[153-156] Alemtuzumab + rituximab results in a higher ORR than that observed with alemtuzumab monotherapy and there was no significant difference in response rates between patients with fludarabine-sensitive and fludarabine-refractory disease.[155] Myelosuppression and infections were the most common grade 3–4 toxicities. However, it should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.[153,156]

Bendamustine and Rituximab ± Idelalisib or Ibrutinib

The BR regimen also has demonstrated activity in patients with relapsed/refractory CLL, resulting in an ORR of 46% in the subgroup of patients with fludarabine-refractory disease.[157] 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.[158,159]

In the HELIOS trial (578 patients with previously treated CLL or SLL), after a median follow-up of 35 months, the median PFS was significantly longer for patients treated with BR + ibrutinib (for 6 months followed by >2 years of continuous ibrutinib) compared to those treated with BR + placebo (not reached vs. 14 months; $P < .0001$).[158] The 36-month PFS rate was 68% and 14%, respectively. The median OS was not reached in either arm but was significantly longer for the BR + ibrutinib ($P = .019$) and the 36-month OS rate was 82% and 73%, 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 + idelalisib versus 11 months for BR + placebo ($P < .0001$).[159] The incidence of opportunistic infections and severe adverse events were more frequent in the idelalisib arm.

BR ± 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

In the phase III randomized REACH trial (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.[160] 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).[161] The ORR was 74% with a CR rate of 30% and the median PFS was 21 months. After a median follow-up of 43 months, the estimated median survival was 47 months. The most common adverse events with FCR were hematologic toxicities, including grade 3 or 4 neutropenia associated with 56% of treatment cycles and grade 3 or 4 thrombocytopenia in 20% of cycles. Pneumonia or sepsis was reported in 16% of patients. The subgroup of patients with fludarabine-refractory disease (n = 54) had a significantly lower ORR (56% vs. 79%; $P < .001$) and CR rate (7% vs. 39%; $P < .001$) compared with fludarabine-sensitive patients; the median PFS (8 months vs. 28 months; $P < .001$) and OS (38 months vs. 52 months; $P < .05$) were also significantly decreased among patients with fludarabine-refractory CLL.[161] 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 11 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.[161]

The PCR regimen is also safe and effective in patients with previously treated CLL, resulting in an ORR of 75% among patients with fludarabine-refractory disease.[162]

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 comorbidities 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 + ofatumumab (n = 183) versus FC alone (n = 182) in patients with relapsed CLL (median age 61 years; 134 patients [37%] >65 years), FC + 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 + ofatumumab and FC ($P = .0032$).[163] 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 + ofatumumab and in 36% of patients treated with FC.

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

HDMP + Rituximab

In small studies, HDMP + 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.[164,165] 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.[164,165]

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

Idelalisib

Idelalisib monotherapy also had clinical activity in relapsed/refractory CLL resulting in an ORR of 72% (39% PR and 33% PR with treatment-induced

lymphocytosis).[76] The median PFS was 16 months and the median OS was not reached, with 75% of patients surviving at 36 months.

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/refractory indolent NHL) showed that idelalisib monotherapy resulted in an ORR of 55% to 61% in the subset of patients with relapsed or refractory SLL.[166] 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.

Lenalidomide ± Rituximab

Lenalidomide ± rituximab is included as an option for relapsed/refractory therapy, regardless of patient's age or comorbidities.[167-169]

In a phase II study of 59 patients with relapsed or refractory CLL, lenalidomide + rituximab resulted in an ORR of 66% with CR in 12%.[167] 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.[168] 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 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.

Monotherapy with Obinutuzumab or Ofatumumab

In the GAUGIN study (n = 20 patients), obinutuzumab at a fixed dose of 1000 mg resulted in a best ORR of 30%, in patients with heavily pretreated relapsed or refractory CLL.[170] The median PFS and duration of response were 11 months and 9 months, respectively.

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.[171] 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.[172] The ORR was 43%, 44%, and 53%, respectively, for CLL with previous rituximab exposure, rituximab-refractory CLL, and rituximab-naive CLL. The median PFS was 5.3, 5.5, and 5.6 months, respectively, and median OS was 15.5, 15.5, and 20 months, respectively.

Monotherapy with obinutuzumab or ofatumumab 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.[173,174] 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.[174] The most common grade 3 or 4 adverse events were neutropenia, thrombocytopenia, anemia, and decreased lymphocyte count. In a post-hoc subgroup analysis of 28 patients enrolled in the aforementioned phase II studies who received >1 BCRi therapy (ibrutinib or idelalisib), venetoclax resulted in higher ORR (75% vs. 43%) and longer PFS (not reached vs. 16 months) in patients who had received only one BCRi compared to those who had received >1 BCRi. The estimated 12-month OS rates were 93% and 89% for patients previously treated with only one BCRi and >1 BCRi, respectively.[175] The results of a retrospective analysis showed that the use of venetoclax was associated with better ORR (79% vs. 46% following failure of idelalisib) and a trend towards improved PFS following failure of ibrutinib compared to failure of idelalisib.[176]

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

Post Second-line Maintenance Therapy

Ofatumumab maintenance or lenalidomide maintenance (category 2B) is included as an option (*Other Recommended Regimens)* in patients who are in CR or PR after second-line chemoimmunotherapy based on the results of the phase III randomized trials (PROLONG trial and CONTINUUM trial).[177,178]

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%.[179] After a median follow-up of 57 months, the estimated 5-year PFS and OS were 74% and 85%, respectively.[180] The cumulative incidence of progression at 24 months was 9%. Grade ≥3 neutropenia, anemia, and thrombocytopenia were reported in 24%, 14%, and 10% of patients, respectively. Grade 3 pneumonia and rash were reported in 6% and 2% of patients, respectively.

Patients with del(17p) CLL were excluded from the RESONATE-2 but 12 patients treated with ibrutinib had *TP53* mutation.[118] In the final analysis of this study, after 6-year follow-up, the median PFS was not reached and the estimated 5-year PFS rate was 56% for this group of patients. However, comparison between ibrutinib and chlorambucil could not be made since only 3 patients in the chlorambucil group has *TP53* mutation.

Acalabrutinib ± obinutuzumab

In the ELEVATE-TN phase III study (discussed above) that demonstrated the efficacy of acalabrutinib ± obinutuzumab in 535 patients with previously untreated CLL, del(17p) and *TP53* mutations were present in 10% and 12% of patients, respectively in the acalabrutinib + obinutuzumab arm.[120] In the acalabrutinib monotherapy arm, del(17p) and *TP53* mutations were present in 9% and 11% of patients, respectively.

The PFS benefit for acalabrutinib ± obinutuzumab was seen across all patient subgroups including those with del(17p) or *TP53* mutation.

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

Venetoclax + Obinutuzumab

In the CLL14 study (discussed above) that demonstrated the efficacy of this combination in 432 patients with previously untreated CLL, del(17p) and *TP53* mutations were present in 9% and 11% of patients, respectively.[116] The undetectable-MRD rate in peripheral blood at 3 months after completion of treatment (71% vs. 7%) and 24-month PFS rate (74% vs. 33%; HR, 0.31) were significantly higher for venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab in patients with del(17p) or *TP53* mutation.

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

First-line Therapy: Other Recommended Regimens

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

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

- Alemtuzumab ± rituximab[181-184]
- HDMP + rituximab[132]
- Obinutuzumab[137]

Relapsed/Refractory Therapy: Preferred Regimens

Acalabrutinib

In the phase II study that evaluated acalabrutinib in relapsed/refractory CLL, acalabrutinib resulted in an ORR of 93% in patients with del(17p) and 90% in those with CK.[146] In the ASCEND trial, PFS benefit for acalabrutinib was seen across all patient subgroups including those with del(17p) or *TP53* mutation.[143]

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

Ibrutinib

Ibrutinib is included with a category 1 recommendation. The results of the RESONATE-17 phase II study confirmed the safety and efficacy of ibrutinib in 145 patients with relapsed or refractory del(17p) CLL.[185] 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.[185] In the RESONATE study, del(17p) (32% and 33%, respectively) and *TP53* mutation (51% and 46%, respectively) were present in similar proportions of patients in the ibrutinib and ofatumumab arm. The final analysis of this study also showed that the presence of del(17p)/*TP53* mutation or CK was not associated with inferior PFS outcomes.[148] In an exploratory analysis that combined data from patients with del(17p) and *TP53* mutation, the median PFS was 41 months for patients with del(17p) and/or *TP53* mutation vs. 57 months for those without del(17p) or *TP53* mutation. Similarly, the median PFS was 41 months for patients with CK compared to 45 months for those without CK.

Venetoclax ± Rituximab

In the phase III randomized MURANO study that compared VenR and BR in patients with relapsed/refractory CLL, VenR was superior to BR in prolonging PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation.[142] Del(17p) and *TP53* mutation were present in 27% and 25% of patients, respectively, in patients randomized to VenR and in 27% and 28% of patients, respectively, in patients randomized to BR.

In a phase II study of 158 patients with relapsed or refractory del(17p) CLL, at a median follow-up of 23 months, venetoclax monotherapy resulted in an ORR of 77% (20% CR and 57% PR).[186] The estimated 24-month PFS and OS rates were 54% and 73%, respectively. The ORR and the estimated 24-month PFS and OS were 63%, 50%, and 55%, respectively, for patients who had received prior BCRi therapy. The ORR was also high (>70%) in all subgroups of patients with additional risk features [eg, fludarabine-refractory status, bulky disease, del(17p), *TP53* mutation]. Neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%) were the most commonly treatment-related adverse events.

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

Duvelisib

In the phase III randomized study (DUO) that evaluated duvelisib for relapsed/refractory CLL (n = 319), del(17p), and/or *TP53* mutation were present in 31 out of 160 patients randomized to duvelisib.[144] 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).[187]

Idelalisib + Rituximab

In the phase III randomized study, IdR significantly prolonged survival in patients with del(17p) or *TP53* mutations compared with those treated with rituximab + placebo.[152] The median OS was 29 months for patients treated with IdR compared to 15 months for those treated with rituximab + placebo. IdR is included as an option with a category 2A recommendation.

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.

- Alemtuzumab ± rituximab[154,155]
- HDMP + Rituximab[188]
- Idelalisib[76]
- Lenalidomide ± Rituximab.[167,168]
- Ofatumumab[189]

Special Considerations for the Use of Small-Molecule Inhibitors

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.[117] 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.[190] Recent reports have indicated the risk for supraventricular arrhythmias and other potentially severe cardiac events in patients treated with ibrutinib.[191,192]

In the ELEVATE-TN trial, atrial fibrillation, hypertension, bleeding of any grade, infections and secondary malignancies were reported in 4%, 5%, 39%, 65% and 3% of patients treated with acalabrutinib, respectively.[120] Grade ≥3 hypertension, bleeding and infection were observed in 2%, 2%, and 14% of patients, respectively. In the ASCEND trial, atrial fibrillation, hypertension, and bleeding of any grade were reported in 5%, 3%, and 26% of patients treated with acalabrutinib, respectively.[143] Grade ≥3 atrial fibrillation, hypertension, and bleeding were observed in 1%, 3%, and 2% of patients, respectively. Headaches commonly observed with acalabrutinib early in the treatment course typically resolve after 1 to 2 months of treatment and generally can be managed with analgesics (eg, acetaminophen) and caffeine supplements.

The benefit and risk of ibrutinib or acalabrutinib should be evaluated in patients requiring anti-platelet or anticoagulant therapies. 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. 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. Transition to alternate therapy should be done as soon as possible since progression may accelerate when ibrutinib or acalabrutinib is stopped. Treatment-free interval should be as short as possible.

Hepatitis B virus (HBV) reactivation and invasive fungal infections have been rarely reported in patients treated with ibrutinib.[193,194] 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.[195] Close monitoring of transaminase levels is essential and concurrent administration of idelalisib or duvelisib with other hepatotoxic drugs should be avoided.

Idelalisib and duvelisib are also associated with increased risk of opportunistic infections and febrile neutropenia. The addition of anti-CD20 mAb or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia.[159] Anti-infective prophylaxis for herpes simplex virus (HSV), pneumocystis jirovecii pneumonia (PJP), and cytomegalovirus (CMV) reactivation are recommended for patients receiving idelalisib or 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.[196] Initiation and accelerated escalation of venetoclax (20–400 mg over 3 weeks) with close inpatient monitoring for TLS can be done to quickly regain disease control in a selected subgroup of patients with high tumor burden, rapid disease progression, or disease relapse after treatment with BCRi therapy.[173,197,198] This accelerated schedule has been explored in a small number of hospitalized patients, who received intensive monitoring and TLS prophylaxis. Additionally, continued treatment with BTKi concurrent with initiation and escalation of venetoclax with discontinuation of BTKi after venetoclax dose escalation to 400 mg daily can be considered.[173,197,198] Recommendations for TLS prophylaxis based on tumor burden are outlined in CSLL-G.

Growth factor support should be considered for patients with neutropenia. Dose reduction may be necessary for patients with persistent neutropenia and limited bone marrow involvement.

Allogeneic Hematopoietic Cell Transplant

Long-term results from several prospective studies have shown that allogeneic hematopoietic cell transplant (HCT) can provide long-term disease control and also overcome the poor prognosis associated with del(17p) and *TP53* mutations.[199-206]

It is understood that studies involving allogeneic HCT are subject to significant selection biases. Nonetheless, at the present time, given the favorable outcome of patients with del(17p) or *TP53* mutation treated with ibrutinib as first-line therapy and the availability of venetoclax as an effective treatment option for relapsed or refractory CLL, allogeneic HCT is not considered as a reasonable treatment option for relapse/refractory CLL after initial purine analogue-based therapy.[207]

Indications for Allogeneic HCT

Allogeneic HCT can be considered for CLL/SLL refractory to small-molecule inhibitor therapy in patients without significant comorbidities. HCT-specific comorbidity index (HCT-CI) could be used for the assessment of comorbidities prior to HCT and to predict the risks of non-relapse mortality and the probabilities of survival after HCT.[208,209]

For patients with CLL/SLL with del(17p) or *TP53* mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if CK (≥3 abnormalities) is present. However, available data suggest that CK (≥5 abnormalities) is associated with inferior OS and EFS following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics.[210]

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.[211-213] 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.[214]

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:[215-221]

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

The incidence of Richter's transformation increases with the number of prior chemoimmunotherapy regimens, and the rate is higher in patients treated with a combination of purine nucleoside analogues and alkylating agents.[221] Richter's transformation has also been reported following treatment with ibrutinib and venetoclax.[222-224] Unlike progressive CLL, Richter's transformation developing after treatment with ibrutinib lacked resistance to *BTK* and *PLCG2* mutations.[223] 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.[224] Further study is needed to determine the exact risk profile and mechanism of Richter's transformation.

CLL with expanded proliferation centers (accelerated CLL) may be diagnosed when proliferation centers in CLL are expanded or fused together and show a high Ki-67 proliferative rate (>40%). Progression to CLL with increased prolymphocytes (CLL-PLL) may occur when there are increased prolymphocytes in the blood (>10%–<55%). Neither of these findings is considered as Richter's transformation, but rather as progression of CLL, associated with a more aggressive disease course.[225]

Diagnosis and Workup

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

The workup of patients with Richter's transformation or progression is similar to that of patients with CLL/SLL and should include history and physical exam with attention to node-bearing areas, including Waldeyer's ring, and the size of liver and spleen, whole-body PET/CT scan, or chest/abdomen/pelvis CT with contrast of diagnostic quality. PET/CT scans are recommended to identify the optimal site for nodal biopsy, and biopsies should be directed to lesions with highest FDG uptake on PET scans.[226-228] 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 mostly treated with chemotherapy or chemoimmunotherapy.[229] 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.[230] Tissue biopsy is required for the definitive diagnosis of Richter's transformation. PET alone is insufficient.

Epstein-Barr virus (EBV) infection has been reported in 16% of patients with Richter's transformation and is associated with a poor outcome.[231] 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.[232] Biopsy specimen should be evaluated for EBV infection using latent membrane protein 1 (LMP1) staining or EBV-encoded RNA in situ hybridization (EBER-ISH).

DLBCL arising from CLL can either be clonally unrelated to CLL (78%) or clonally related to CLL (22%).[220,233] 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).[220] The majority of patients with Richter's transformation to clonally related DLBCL carry unmutated *IGHV.*[233] 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.[220,233]

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.[214] 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.[214] 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, and prednisone) resulted in an ORR of 67% (7% CR).[234] 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, prednisone, vincristine, cyclophosphamide, and doxorubicin), the ORR was 39% (17 out of the 44 patients evaluable for treatment response).[235] After a median follow-up of 39 months, the median PFS and OS were 4 months and 6 months, respectively. CK was associated with significantly shorter PFS and OS. The estimated 1-year OS rate was 71% for patients without a CK.

The modified R-hyper-CVAD regimen (rituximab, cyclophosphamide, vincristine, liposomal daunorubicin, and 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%.[236] However, it was associated with significant toxicity (grade 3 neutropenia was the most common hematologic toxicity) and was not more effective than an alternate hyper-CVAD regimen (did not include methotrexate, cytarabine, rituximab, or growth factor support) that was evaluated in an earlier study.[237]

The 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, the OFAR regimen (increasing doses of oxaliplatin, fludarabine, cytarabine, and rituximab) resulted in an ORR of 50%.[238] 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%.[239] Grade 3/4 neutropenia and thrombocytopenia were the most common hematologic toxicities occurring in 80% of patients with both schedules of the OFAR regimen.

R-CHOP, R-EPOCH, R-hyper-CVAD, 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.[214,240,241] 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; $P = .019$).[214] 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.[240] In a

multivariate analysis, chemotherapy-sensitive disease and reduced-intensity conditioning were found to be associated with superior RFS after allogeneic HCT. Autologous HCT may also be appropriate for patients with disease responding to initial therapy but who are not candidates for allogeneic HCT due to age, comorbidities, or lack of a suitable donor.[240]

There are no effective treatment options for patients with Richter's transformation refractory to chemoimmunotherapy. Clinical trial is the preferred treatment option if available. Preliminary data from ongoing clinical trials suggest that anti-programmed cell death protein 1 (PD-1) mAbs (nivolumab and pembrolizumab) have promising activity in patients with Richter's transformation.[242-244]

In a phase I/II study that included 20 patients with Richter's transformation, nivolumab + ibrutinib resulted in an ORR of 65% and the median PFS was 4 months.[243] Diarrhea (33%), neutropenia (31%), and fatigue (26%) of any grade were the most common treatment-related adverse events. Neutropenia (28%) and anemia (23%) were the most common grade 3 or 4 adverse events and the incidence of grade 3 or 4 anemia was 35% in patients with Richter's transformation. In another phase II study of 25 patients (16 patients with relapsed CLL and 9 patients with Richter's transformation to DLBCL), the use of pembrolizumab as a single agent resulted in an ORR of 44% in patients with Richter's transformation and the median PFS and OS were 5 months and 11 months, respectively.[244] Thrombocytopenia (20%), anemia (20%), neutropenia (20%), and dyspnea and hypoxia (8% each) were the most common grade 3 or 4 adverse events.

The panel acknowledged that there are limited published data supporting the use of nivolumab and pembrolizumab in patients with Richter's transformation refractory to chemoimmunotherapy or in patients with a del(17p)/*TP53* mutation and that additional data will be forthcoming. However, some panel members felt that given the unmet clinical need and the lack of effective treatment options, inclusion of PD-1 mAbs (nivolumab and pembrolizumab) as a treatment option is reasonable (based on the data discussed above) for patients with Richter's transformation refractory to chemoimmunotherapy (especially if considering allogeneic HCT). In addition, some panel members pointed out that these agents would also be appropriate as an initial treatment option for patients with del (17p) or *TP53* mutation and for those who are unable to receive chemoimmunotherapy regimens. Few panel members felt that monotherapy with PD-1 mAbs (nivolumab or pembrolizumab) is not an effective treatment option for patients with relapsed or refractory Richter's transformation outside of a clinical trial, citing a recent report in which the use of PD-1 mAbs for the treatment of relapsed/refractory Richter's transformation in a non-trial population (10 patients with biopsy-proven Richter's transformation to DLBCL and all patients had received prior therapy with BTKi) was associated with poor efficacy with a short TTTF.[245]

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

Richter's Transformation to Hodgkin Lymphoma

Richter's transformation to HL is clinically less aggressive than Richter's transformation to DLBCL but it is associated with a poorer prognosis than de novo HL.[212,213,246] Richter's transformation to HL should be managed as outlined in the NCCN Guidelines for Hodgkin Lymphoma. ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) was the most commonly used regimen resulting in an ORR of 68%, and achievement of CR to the ABVD regimen was the most important factor predicting survival of patients with Richter's transformation to HL.[247,248]

CLL-PLL or Accelerated CLL

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

Supportive Care

Infections

Infectious complications are influenced by the progressive reduction in immunoglobulin levels (hypogammaglobulinemia) and are more common in patients with previously treated CLL.[249,250] Patients with heavily pretreated fludarabine-refractory CLL have high susceptibility to developing serious infections.[251]

IVIG is associated with a significant decrease in the occurrence of infections but with no improvement in OS outcome.[252-256] 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.[257] 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.[258,259]

Hepatitis B Virus Reactivation

HBV reactivation has been reported in patients treated with chemotherapy ± immunotherapy agents.[260,261] HBV carriers have a high risk of HBV reactivation. Fulminant hepatitis, hepatic failure, and death associated with HBV reactivation have occurred in patients receiving anti-CD20 mAb -containing regimens, including rituximab, obinutuzumab, or ofatumumab.[262] 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.[263]

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.[264,265] Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. During the treatment period, viral load should be monitored monthly with PCR and then every 3 months after completion of treatment. If viral load is consistently undetectable, prophylaxis with antivirals should be continued. If viral load fails to drop or a previously undetectable PCR becomes

positive, consultation with a hepatologist and discontinuation of anti-CD20 mAb is recommended. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of treatment.[266]

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.[267] 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.[268,269] 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.[270,271] Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias.

Although the direct antiglobulin test (DAT) was used for the diagnosis of AIHA, most patients with AIHA have a negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA.[272] 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.[272-275] 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.[272,276] 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.[277] 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.[277]

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine,[278] and splenectomy should be used in steroid-refractory cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias.[279-285] Romiplostim and eltrombopag have shown promising results in the treatment of thrombocytopenia associated with ITP.[286-289] 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.[271] 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.[271]

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.[290-292] Tumor flare was more frequent among patients with enlarged (>5 cm) lymph nodes at baseline.[290] 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).[293] 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).[168,294]

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.[290,295] Prophylaxis with daily low-dose aspirin (81 mg daily) may be considered in patients with extremely high platelet counts at baseline. Patients already on anticoagulants, such as warfarin, do not need aspirin. However, it should be noted that these recommendations may differ from the NCCN Guidelines for Venous Thromboembolic Disease in which the recommendations for VTE associated with lenalidomide pertain only to patients with multiple myeloma.

Tumor Lysis Syndrome

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

Management of Intolerance to anti-CD20 Monoclonal Antibody Therapy

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

A rapid infusion over 90 minutes can be used if no severe infusion-related reactions were experienced with the prior cycle of rituximab. Re-challenge with the same anti-CD20 mAb is not recommended in patients experiencing aforementioned severe reactions to the chosen anti-CD20 mAb (rituximab, obinutuzumab, or ofatumumab). There are some data (based on clinical experience) showing that substitution with an alternative anti-CD20 mAb is tolerated in patients experiencing severe reactions to a specific anti-CD20 mAb; however, it is unclear if such a substitution poses the same risk of recurrence.[296,297]

Rituximab and hyaluronidase human injection for subcutaneous use is approved by the FDA for the treatment of patients with CLL based on the results of the SAWYER trial in which subcutaneous rituximab (rituximab with recombinant human hyaluronidase) had similar pharmacokinetic characteristics as IV rituximab when used in combination with fludarabine and cyclophosphamide.[298] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for intravenous rituximab in

patients who have received at least one full dose of intravenous rituximab without experiencing severe adverse reactions.

Summary

The choice of first-line treatment for CLL/SLL should be based on the disease stage, presence or absence of del(17p) or *TP53* mutation, *IGHV* mutation status (if considering chemoimmunotherapy), patient's age, performance status, comorbid conditions, and the agent's toxicity profile. Ibrutinib and acalabrutinib ± obinutuzumab are preferred first-line therapy options for all patients including in high-risk subgroups such as those with del(11q) or del(17p)/*TP53* mutation and unmutated *IGHV*. Venetoclax + obinutuzumab is an effective fixed-duration chemotherapy-free first-line treatment option for all patients including those with del(17p)/*TP53* mutation. Idelalisib is not indicated in first-line treatment. FCR is preferred for patients <65 years with untreated *IGHV*-mutated CLL as it offers a defined treatment course and the majority of patients with *IGHV*-mutated CLL who receive first-line FCR are expected to have more than 10 years of PFS, and may potentially be cured of their disease. Ibrutinib, idelalisib (± 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 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.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30620402.

2. Tsimberidou AM, Wen S, O'Brien S, et al. Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2007;25:4648-4656. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17925562.

3. U.S. National library of medicine key medline® indicators Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

4. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46:219-234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1139039.

5. Binet J, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7237385.

6. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of hodgkin and non-hodgkin lymphoma: The Lugano classification. J Clin Oncol 2014;32:3059-3068. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25113753.

7. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999;94:1840-1847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10477712.

8. Hamblin TJ, Davis Z, Gardiner A, et al. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood 1999;94:1848-1854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10477713.

9. Tobin G, Thunberg U, Johnson A, et al. Somatically mutated Ig V(H)3-21 genes characterize a new subset of chronic lymphocytic leukemia. Blood 2002;99:2262-2264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11877310.

10. Oscier DG, Gardiner AC, Mould SJ, et al. Multivariate analysis of prognostic factors in CLL: Clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. Blood 2002;100:1177-1184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149195.

11. Krober A, Seiler T, Benner A, et al. V(H) mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood 2002;100:1410-1416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12149225.

12. Krober A, Bloehdorn J, Hafner S, et al. Additional genetic high-risk features such as 11q deletion, 17p deletion, and V3-21 usage characterize discordance of ZAP-70 and vh mutation status in chronic lymphocytic leukemia. J Clin Oncol 2006;24:969-975. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16418492.

13. Oscier D, Wade R, Davis Z, et al. Prognostic factors identified three risk groups in the LRF CLL4 trial, independent of treatment allocation. Haematologica 2010;95:1705-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20511662.

14. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910-1916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11136261.

15. Tsimberidou AM, Tam C, Abruzzo LV, et al. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. Cancer

2009;115:373-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19117034.

16. Tam CS, Shanafelt TD, Wierda WG, et al. De novo deletion 17p13.1 chronic lymphocytic leukemia shows significant clinical heterogeneity: The M. D. Anderson and Mayo Clinic experience. Blood 2009;114:957-964. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19414856.

17. Van Dyke DL, Werner L, Rassenti LZ, et al. The dohner fluorescence in situ hybridization prognostic classification of chronic lymphocytic leukaemia (CLL): The CLL research consortium experience. Br J Haematol 2016;173:105-113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26848054.

18. Stilgenbauer S, Sander S, Bullinger L, et al. Clonal evolution in chronic lymphocytic leukemia: Acquisition of high-risk genomic aberrations associated with unmutated vh, resistance to therapy, and short survival. Haematologica 2007;92:1242-1245. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17666364.

19. Rossi D, Cerri M, Deambrogi C, et al. The prognostic value of TP53 mutations in chronic lymphocytic leukemia is independent of del17p13: Implications for overall survival and chemorefractoriness. Clin Cancer Res 2009;15:995-1004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188171.

20. Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol 2010;28:4473-4479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20697090.

21. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: Results from the CLL8 trial. Blood 2014;123:3247-3254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24652989.

22. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med 2018;379:2517-2528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30501481.

23. Woyach JA, Ruppert AS, Heerema NA, et al. Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: Long-term follow-up of CALGB study 9712. J Clin Oncol 2011;29:1349-1355. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21321292.

24. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: Updated results of the CLL8 trial. Blood 2016;127:208-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26486789.

25. Bulian P, Shanafelt TD, Fegan C, et al. Cd49d is the strongest flow cytometry-based predictor of overall survival in chronic lymphocytic leukemia. J Clin Oncol 2014;32:897-904. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24516016.

26. Baumann T, Delgado J, Santacruz R, et al. CD49d (ITGA4) expression is a predictor of time to first treatment in patients with chronic lymphocytic leukaemia and mutated IGHV status. Br J Haematol 2016;172:48-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26559905.

27. Dal Bo M, Bulian P, Bomben R, et al. CD49d prevails over the novel recurrent mutations as independent prognosticator of overall survival in chronic lymphocytic leukemia. Leukemia 2016;30:2011-2018. Available at:

28. Strati P, Parikh SA, Chaffee KG, et al. CD49d associates with nodal presentation and subsequent development of lymphadenopathy in patients with chronic lymphocytic leukaemia. Br J Haematol 2017;178:99-105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28386906.

29. Gooden CE, Jones P, Bates R, et al. CD49d shows superior performance characteristics for flow cytometric prognostic testing in chronic lymphocytic leukemia/small lymphocytic lymphoma. Cytometry B Clin Cytom 2018;94:129-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27221715.

30. Del Poeta G, Maurillo L, Venditti A, et al. Clinical significance of CD38 expression in chronic lymphocytic leukemia. Blood 2001;98:2633-2639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11675331.

31. Ibrahim S, Keating M, Do KA, et al. CD38 expression as an important prognostic factor in B-cell chronic lymphocytic leukemia. Blood 2001;98:181-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11418478.

32. Gentile M, Mauro FR, Calabrese E, et al. The prognostic value of CD38 expression in chronic lymphocytic leukaemia patients studied prospectively at diagnosis: A single institute experience. Br J Haematol 2005;130:549-557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16098069.

33. Crespo M, Bosch F, Villamor N, et al. ZAP-70 expression as a surrogate for immunoglobulin-variable-region mutations in chronic lymphocytic leukemia. N Engl J Med 2003;348:1764-1775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12724482.

34. Wiestner A, Rosenwald A, Barry TS, et al. ZAP-70 expression identifies a chronic lymphocytic leukemia subtype with unmutated immunoglobulin genes, inferior clinical outcome, and distinct gene expression profile. Blood 2003;101:4944-4951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12595313.

35. Orchard JA, Ibbotson RE, Davis Z, et al. ZAP-70 expression and prognosis in chronic lymphocytic leukaemia. Lancet 2004;363:105-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14726163.

36. Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. N Engl J Med 2004;351:893-901. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15329427.

37. Del Principe MI, Del Poeta G, Buccisano F, et al. Clinical significance of ZAP-70 protein expression in B-cell chronic lymphocytic leukemia. Blood 2006;108:853-861. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16601244.

38. Rassenti LZ, Jain S, Keating MJ, et al. Relative value of ZAP-70, CD38, and immunoglobulin mutation status in predicting aggressive disease in chronic lymphocytic leukemia. Blood 2008;112:1923-1930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18577710.

39. Corcoran M, Parker A, Orchard J, et al. ZAP-70 methylation status is associated with ZAP-70 expression status in chronic lymphocytic leukemia. Haematologica 2005;90:1078-1088. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16079107.

40. Claus R, Lucas DM, Stilgenbauer S, et al. Quantitative DNA methylation analysis identifies a single CPG dinucleotide important for ZAP-70 expression and predictive of prognosis in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2483-2491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22564988.

41. Claus R, Lucas DM, Ruppert AS, et al. Validation of ZAP-70 methylation and its relative significance in predicting outcome in chronic lymphocytic leukemia. Blood 2014;124:42-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24868078.

42. Wierda WG, O'Brien S, Wang X, et al. Characteristics associated with important clinical end points in patients with chronic lymphocytic leukemia at initial treatment. J Clin Oncol 2009;27:1637-1643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19224852.

43. Thompson PA, O'Brien SM, Xiao L, et al. Beta2 -microglobulin normalization within 6 months of ibrutinib-based treatment is associated with superior progression-free survival in patients with chronic lymphocytic leukemia. Cancer 2016;122:565-573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26588193.

44. Fabbri G, Rasi S, Rossi D, et al. Analysis of the chronic lymphocytic leukemia coding genome: Role of NOTCH1 mutational activation. J Exp Med 2011;208:1389-1401. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21670202.

45. Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. Nature 2011;475:101-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21642962.

46. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. N Engl J Med 2011;365:2497-2506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22150006.

47. Quesada V, Conde L, Villamor N, et al. Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. Nat Genet 2012;44:47-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22158541.

48. Rossi D, Fangazio M, Rasi S, et al. Disruption of BIRC3 associates with fludarabine chemorefractoriness in TP53 wild-type chronic lymphocytic leukemia. Blood 2012;119:2854-2862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22308293.

49. Rossi D, Rasi S, Fabbri G, et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukemia. Blood 2012;119:521-529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22077063.

50. Schnaiter A, Paschka P, Rossi M, et al. NOTCH1, SF3B1, and TP53 mutations in fludarabine-refractory CLL patients treated with alemtuzumab: Results from the CLL2H trial of the GCLLSG. Blood 2013;122:1266-1270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23821658.

51. Oscier DG, Rose-Zerilli MJ, Winkelmann N, et al. The clinical significance of NOTCH1 and SF3B1 mutations in the UK LRF CLL4 trial. Blood 2013;121:468-475. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23086750.

52. Messina M, Del Giudice I, Khiabanian H, et al. Genetic lesions associated with chronic lymphocytic leukemia chemo-refractoriness. Blood 2014;123:2378-2388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24550227.

53. Wierda WG, O'Brien S, Wang X, et al. Prognostic nomogram and index for overall survival in previously untreated patients with chronic lymphocytic leukemia. Blood 2007;109:4679-4685. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17299097.

54. Shanafelt TD, Jenkins G, Call TG, et al. Validation of a new prognostic index for patients with chronic lymphocytic leukemia. Cancer 2009;115:363-372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19090008.

55. Molica S, Mauro FR, Callea V, et al. The utility of a prognostic index for predicting time to first treatment in early chronic lymphocytic leukemia: The gimema experience. Haematologica 2010;95:464-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19903673.

56. Wierda WG, O'Brien S, Wang X, et al. Multivariable model for time to first treatment in patients with chronic lymphocytic leukemia. J Clin Oncol 2011;29:4088-4095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969505.

57. Rossi D, Rasi S, Spina V, et al. Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. Blood 2013;121:1403-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23243274.

58. Visentin A, Facco M, Frezzato F, et al. Integrated CLL Scoring System, a New and Simple Index to Predict Time to Treatment and Overall Survival in Patients With Chronic Lymphocytic Leukemia. Clin Lymphoma Myeloma Leuk 2015;15:612-620 e611-615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26233718.

59. International CLLIPIwg. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol 2016;17:779-790. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27185642.

60. Gentile M, Shanafelt TD, Rossi D, et al. Validation of the CLL-IPI and comparison with the MDACC prognostic index in newly diagnosed patients. Blood 2016;128:2093-2095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27549308.

61. Gentile M, Shanafelt TD, Mauro FR, et al. Predictive value of the CLL-IPI in CLL patients receiving chemo-immunotherapy as first-line treatment. Eur J Haematol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30039576.

62. Ahn IE, Farber CM, Davids MS, et al. Early progression of disease as a predictor of survival in chronic lymphocytic leukemia. Blood Adv 2017;1:2433-2443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29296893.

63. Baliakas P, Iskas M, Gardiner A, et al. Chromosomal translocations and karyotype complexity in chronic lymphocytic leukemia: A systematic reappraisal of classic cytogenetic data. Am J Hematol 2014;89:249-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24166834.

64. Thompson PA, O'Brien SM, Wierda WG, et al. Complex karyotype is a stronger predictor than del(17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens. Cancer 2015;121:3612-3621. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26193999.

65. Blanco G, Puiggros A, Baliakas P, et al. Karyotypic complexity rather than chromosome 8 abnormalities aggravates the outcome of chronic lymphocytic leukemia patients with TP53 aberrations. Oncotarget 2016;7:80916-80924. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27821812.

66. Le Bris Y, Struski S, Guieze R, et al. Major prognostic value of complex karyotype in addition to TP53 and IGHV mutational status in first-line chronic lymphocytic leukemia. Hematol Oncol 2017;35:664-670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27678008.

67. Puiggros A, Collado R, Calasanz MJ, et al. Patients with chronic lymphocytic leukemia and complex karyotype show an adverse outcome even in absence of TP53/ATM FISH deletions. Oncotarget 2017;8:54297-54303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28903342.

68. Baliakas P, Jeromin S, Iskas M, et al. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. Blood 2019;133:1205-1216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30602617.

69. Woyach JA, Ruppert AS, Guinn D, et al. BTKC481S-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia. J Clin Oncol 2017;35:1437-1443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28418267.

70. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the bruton's tyrosine kinase inhibitor ibrutinib. N Engl J Med 2014;370:2286-2294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24869598.

71. Ahn IE, Underbayev C, Albitar A, et al. Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia. Blood 2017;129:1469-1479. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28049639.

72. Woyach J, Huang Y, Rogers K, et al. Resistance to Acalabrutinib in CLL Is Mediated Primarily By BTK Mutations [abstract]. Blood 2019;134:Abstract 504. Available at: https://ash.confex.com/ash/2019/webprogram/Paper127674.html.

73. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29540348.

74. Chanan-Khan A, Miller KC, Lawrence D, et al. Tumor flare reaction associated with lenalidomide treatment in patients with chronic lymphocytic leukemia predicts clinical response. Cancer 2011;117:2127-2135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21523725.

75. Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. Blood

2014;123:1810-1817. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24415539.

76. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. Blood 2014;123:3390-3397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24615777.

77. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:323-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26641137.

78. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22778323.

79. Kovacs G, Robrecht S, Fink AM, et al. Minimal Residual Disease Assessment Improves Prediction of Outcome in Patients With Chronic Lymphocytic Leukemia (CLL) Who Achieve Partial Response: Comprehensive Analysis of Two Phase III Studies of the German CLL Study Group. J Clin Oncol 2016;34:3758-3765. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27573660.

80. Thompson PA, Peterson CB, Strati P, et al. Serial minimal residual disease (MRD) monitoring during first-line FCR treatment for CLL may direct individualized therapeutic strategies. Leukemia 2018;32:2388-2398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29769624.

81. Molica S, Giannarelli D, Montserrat E. Minimal Residual Disease and Survival Outcomes in Patients With Chronic Lymphocytic Leukemia: A Systematic Review and Meta-analysis. Clin Lymphoma Myeloma Leuk 2019;19:423-430. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31027992.

82. Fischer K, Ritgen M, Al-Sawaf O, et al. Quantitative Analysis of Minimal Residual Disease (MRD) Shows High Rates of Undetectable MRD after Fixed-Duration Chemotherapy-Free Treatment and Serves As Surrogate Marker for Progression-Free Survival: A Prospective Analysis of the Randomized CLL14 Trial [abstract]. Blood 2019;134:Abstract 36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31724026.

83. Rawstron AC, Bottcher S, Letestu R, et al. Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual disease monitoring in CLL. Leukemia 2013;27:142-149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23041722.

84. Rawstron AC, Fazi C, Agathangelidis A, et al. A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study. Leukemia 2016;30:929-936. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26639181.

85. Logan AC, Gao H, Wang C, et al. High-throughput VDJ sequencing for quantification of minimal residual disease in chronic lymphocytic leukemia and immune reconstitution assessment. Proc Natl Acad Sci U S A 2011;108:21194-21199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22160699.

86. Aw A, Kim HT, Fernandes SM, et al. Minimal residual disease detected by immunoglobulin sequencing predicts CLL relapse more effectively than flow cytometry. Leuk Lymphoma 2018;59:1986-1989. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29164966.

87. Gutierrez A, Jr., Tschumper RC, Wu X, et al. LEF-1 is a prosurvival factor in chronic lymphocytic leukemia and is expressed in the preleukemic state of monoclonal B-cell lymphocytosis. Blood 2010;116:2975-2983. Available at:

88. Palumbo GA, Parrinello N, Fargione G, et al. CD200 expression may help in differential diagnosis between mantle cell lymphoma and B-cell chronic lymphocytic leukemia. Leuk Res 2009;33:1212-1216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19230971.

89. Sandes AF, de Lourdes Chauffaille M, Oliveira CR, et al. CD200 has an important role in the differential diagnosis of mature B-cell neoplasms by multiparameter flow cytometry. Cytometry B Clin Cytom

2014;86:98-105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24243815.

90. Menter T, Dirnhofer S, Tzankov A. LEF1: a highly specific marker for the diagnosis of chronic lymphocytic B cell leukaemia/small lymphocytic B cell lymphoma. J Clin Pathol 2015;68:473-478. Available at:

91. Dicker F, Schnittger S, Haferlach T, et al. Immunostimulatory oligonucleotide-induced metaphase cytogenetics detect chromosomal aberrations in 80% of CLL patients: A study of 132 CLL cases with correlation to FISH, IGVH status, and CD38 expression. Blood 2006;108:3152-3160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16840733.

92. Heerema NA, Byrd JC, Dal Cin PS, et al. Stimulation of chronic lymphocytic leukemia cells with CPG oligodeoxynucleotide gives consistent karyotypic results among laboratories: A CLL research consortium (CRC) study. Cancer Genet Cytogenet 2010;203:134-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21156225.

93. Davis Z, Forconi F, Parker A, et al. The outcome of Chronic lymphocytic leukaemia patients with 97% IGHV gene identity to germline is distinct from cases with <97% identity and similar to those with 98% identity. Br J Haematol 2016;173:127-136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26846718.

94. Jain P, Nogueras Gonzalez GM, Kanagal-Shamanna R, et al. The absolute percent deviation of IGHV mutation rather than a 98% cut-off predicts survival of chronic lymphocytic leukaemia patients treated with fludarabine, cyclophosphamide and rituximab. Br J Haematol 2018;180:33-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29164608.

95. Tobin G, Thunberg U, Laurell A, et al. Patients with chronic lymphocytic leukemia with mutated VH genes presenting with Binet stage B or C form a subgroup with a poor outcome. Haematologica 2005;90:465-469. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15820941.

96. Morabito F, Shanafelt TD, Gentile M, et al. Immunoglobulin heavy chain variable region gene and prediction of time to first treatment in patients with chronic lymphocytic leukemia: Mutational load or mutational status? Analysis of 1003 cases. Am J Hematol 2018;93:E216-E219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29984867.

97. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. Blood 2016;127:303-309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26492934.

98. Hamblin TJ, Orchard JA, Ibbotson RE, et al. CD38 expression and immunoglobulin variable region mutations are independent prognostic variables in chronic lymphocytic leukemia, but CD38 expression may vary during the course of the disease. Blood 2002;99:1023-1029. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11807008.

99. Rawstron AC, Bennett FL, O'Connor SJ, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Engl J Med 2008;359:575-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18687638.

100. Rossi D, Sozzi E, Puma A, et al. The prognosis of clinical monoclonal B cell lymphocytosis differs from prognosis of Rai 0 chronic lymphocytic leukaemia and is recapitulated by biological risk factors. Br J Haematol 2009;146:64-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19438485.

101. Marti GE, Rawstron AC, Ghia P, et al. Diagnostic criteria for monoclonal B-cell lymphocytosis. Br J Haematol 2005;130:325-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16042682.

102. Rawstron AC, Shanafelt T, Lanasa MC, et al. Different biology and clinical outcome according to the absolute numbers of clonal B-cells in monoclonal B-cell lymphocytosis (MBL). Cytometry B Clin Cytom 2010;78 Suppl 1:S19-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20839333.

103. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-2390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26980727.

104. Shanafelt TD, Kay NE, Rabe KG, et al. Brief report: natural history of individuals with clinically recognized monoclonal B-cell lymphocytosis compared with patients with Rai 0 chronic lymphocytic leukemia. J Clin Oncol 2009;27:3959-3963. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19620484.

105. Gibson SE, Swerdlow SH, Ferry JA, et al. Reassessment of small lymphocytic lymphoma in the era of monoclonal B-cell lymphocytosis. Haematologica 2011;96:1144-1152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21546505.

106. Conte MJ, Bowen DA, Wiseman GA, et al. Use of positron emission tomography-computed tomography in the management of patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Leuk Lymphoma 2014;55:2079-2084. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24286263.

107. Falchi L, Keating MJ, Marom EM, et al. Correlation between FDG/PET, histology, characteristics, and survival in 332 patients with chronic lymphoid leukemia. Blood 2014;123:2783-2790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24615780.

108. U.S. Food and Drug Administration: Biosimilar and Interchangeable Products. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm.

109. U.S. Food and Drug Administration: Biosimilar Development, Review, and Approval. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580429.htm.

110. Kim WS, Buske C, Ogura M, et al. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 compared with rituximab in patients with previously untreated advanced-stage follicular lymphoma: a randomised, double-blind, parallel-group, non-inferiority phase 3 trial. Lancet Haematol 2017;4:e362-e373. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28712940.

111. Ogura M, Sancho JM, Cho SG, et al. Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 in comparison with rituximab in patients with previously untreated low-tumour-burden follicular lymphoma: a randomised, double-blind, parallel-group, phase 3 trial. Lancet Haematol 2018;5:e543-e553. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30389036.

112. Sharman J, Liberati AM, Santucci Silva R, et al. A randomized, double-blind efficacy and safety study of PF-05280586 (a potential rituximab biosimilar) compared with rituximab reference product (MabThera) in subjects with previously untreated CD20-positive, low tumor burden follicular lymphoma (LTB-FL) [abstract]. Blood 2018;132:Abstract 394. Available at: http://www.bloodjournal.org/content/132/Suppl_1/394.abstract.

113. Woyach JA, Ruppert AS, Rai K, et al. Impact of age on outcomes after initial therapy with chemotherapy and different chemoimmunotherapy regimens in patients with chronic lymphocytic leukemia: Results of sequential cancer and leukemia group b studies. J Clin Oncol 2013;31:440-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23233702.

114. Goede V, Cramer P, Busch R, et al. Interactions between comorbidity and treatment of chronic lymphocytic leukemia: Results of German Chronic Lymphocytic Leukemia Study Group trials. Haematologica 2014;99:1095-1100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24584349.

115. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18811613.

116. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med 2019;380:2225-2236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31166681.

117. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 2015;373:2425-2437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26639149.

118. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia 2019:[Epub ahead of print]. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31628428.

119. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med 2019;381:432-443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31365801.

120. Sharman JP, Banerji V, Fogliatto LM, et al. ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab (O) or Alone Vs O Plus Chlorambucil (Clb) in Patients (Pts) with Treatment-Naive Chronic Lymphocytic Leukemia (CLL) [abstract]. Blood 2019;134:Abstract 31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31724010.

121. Michallet AS, Aktan M, Hiddemann W, et al. Rituximab plus bendamustine or chlorambucil for chronic lymphocytic leukemia: primary analysis of the randomized, open-label MABLE study. Haematologica 2018;103:698-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29419437.

122. Flinn IW, Panayiotidis P, Afanasyev B, et al. A phase 2, multicenter study investigating ofatumumab and bendamustine combination in patients with untreated or relapsed CLL. Am J Hematol 2016;91:900-906. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27222473.

123. Stilgenbauer S, Leblond V, Foa R, et al. Obinutuzumab plus bendamustine in previously untreated patients with CLL: a subgroup analysis of the GREEN study. Leukemia 2018;32:1778-1786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29749403.

124. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): An international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2016;17:928-942. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27216274.

125. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia 2015;29:1602-1604. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25634683.

126. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:43-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30522969.

127. Shanafelt TD, Wang V, Kay NE, et al. Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia (CLL): Extended Follow-up from the E1912 Trial [abstract]. Blood 2019;134:Abstract 33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31723996.

128. Cazin B, Divine M, Lepretre S, et al. High efficacy with five days schedule of oral fludarabine phosphate and cyclophosphamide in patients with previously untreated chronic lymphocytic leukaemia. Br J Haematol 2008;143:54-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18710390.

129. Dearden CE, Richards S, Else M, et al. A comparison of the efficacy and safety of oral and intravenous fludarabine in chronic lymphocytic leukemia in the LRF CLL4 trial. Cancer 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21157963.

130. Rossi JF, van Hoof A, de Boeck K, et al. Efficacy and safety of oral fludarabine phosphate in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2004;22:1260-1267. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15051774.

131. Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: Results from cancer and leukemia group b 9712 (CALGB 9712). Blood 2003;101:6-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12393429.

132. Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia 2009;23:1779-1789. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19693094.

133. Burger JA, Sivina M, Jain N, et al. Randomized trial of ibrutinib vs ibrutinib plus rituximab in patients with chronic lymphocytic leukemia. Blood 2019;133:1011-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30530801.

134. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated b chronic lymphocytic leukemia. Blood 2007;109:405-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17008537.

135. Kay NE, Wu W, Kabat B, et al. Pentostatin and rituximab therapy for previously untreated patients with B-cell chronic lymphocytic leukemia. Cancer 2010;116:2180-2187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20187101.

136. Reynolds C, Di Bella N, Lyons RM, et al. A phase III trial of fludarabine, cyclophosphamide, and rituximab vs. Pentostatin, cyclophosphamide, and rituximab in B-cell chronic lymphocytic leukemia. Invest New Drugs 2012;30:1232-1240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21922186.

137. Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. Blood 2016;127:79-86. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26472752.

138. Hainsworth JD, Litchy S, Barton JH, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: A phase II trial of the minnie pearl cancer research network. J Clin Oncol 2003;21:1746-1751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12721250.

139. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009;114:3382-3391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19605849.

140. Fink AM, Bahlo J, Robrecht S, et al. Lenalidomide maintenance after first-line therapy for high-risk chronic lymphocytic leukaemia (CLLM1): final results from a randomised, double-blind, phase 3 study. Lancet Haematol 2017;4:e475-e486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28916311.

141. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371:213-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24881631.

142. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia. N Engl J Med 2018;378:1107-1120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29562156.

143. Ghia P, Pluta A, Wach M, et al. ASCEND phase 3 study of acalabrutinib vs investigator's choice of rituximab plus idelalisib (IDR) or bendamustine (BR) In patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) [abstract]. European Hematology Association Congress; 2019:Abstract LB2606. Available at:

144. Flinn IW, Hillmen P, Montillo M, et al. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood 2018;132:2446-2455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30287523.

145. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370:997-1007. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24450857.

146. Furman RR, Wierda WG, Schuh A, et al. Acalabrutinib Monotherapy in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: 42-Month Follow-up of a Phase 2 Study [abstract]. Blood 2019;134:Abstract 3039. Available at:

147. Awan FT, Schuh A, Brown JR, et al. Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib. Blood Adv 2019;3:1553-1562. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31088809.

148. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. Am J Hematol 2019: [Epub ahead of print]. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31512258.

149. Kater AP, Seymour JF, Hillmen P, et al. Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study. J Clin Oncol 2019;37:269-277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30523712.

150. Davids MS, Kuss BJ, Hillmen P, et al. The efficacy and safety of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL or SLL: updated results from the DUO crossover extension study [abstract]. Blood 2018;132:Abstract 3140. Available at: http://www.bloodjournal.org/content/132/Suppl_1/3140.abstract.

151. Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients With Refractory Indolent Non-Hodgkin Lymphoma. J Clin Oncol 2019;37:912-922. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30742566.

152. Sharman JP, Coutre SE, Furman RR, et al. Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. J Clin Oncol 2019;37:1391-1402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30995176.

153. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: Results of a large international study. Blood 2002;99:3554-3561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11986207.

154. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: Clinical results and prognostic marker analyses from the CLL2H study of the german chronic lymphocytic leukemia study group. J Clin Oncol 2009;27:3994-4001. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19597025.

155. Faderl S, Ferrajoli A, Wierda W, et al. Alemtuzumab by continuous intravenous infusion followed by subcutaneous injection plus rituximab in the treatment of patients with chronic lymphocytic leukemia recurrence. Cancer 2010;116:2360-2365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20225334.

156. Fiegl M, Stauder R, Steurer M, et al. Alemtuzumab in chronic lymphocytic leukemia: Final results of a large observational multicenter study in mostly pretreated patients. Ann Hematol 2014;93:267-277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24292560.

157. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A multicenter phase II trial of the german chronic lymphocytic leukemia study group. J Clin Oncol 2011:3559-3566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21844497.

158. Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. Leukemia 2019;33:969-980. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30315239.

159. Zelenetz AD, Barrientos JC, Brown JR, et al. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 2017;18:297-311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28139405.

160. Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756-1765. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20194844.

161. Badoux XC, Keating MJ, Wang X, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood 2011;117:3016-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21245487.

162. Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24:1575-1581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16520464.

163. Robak T, Warzocha K, Govind Babu K, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: Results from the COMPLEMENT 2 trial. Leuk Lymphoma 2016:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27731748.

164. Castro JE, Sandoval-Sus JD, Bole J, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. Leukemia 2008;22:2048-2053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18754025.

165. Dungarwalla M, Evans SO, Riley U, et al. High dose methylprednisolone and rituximab is an effective therapy in advanced refractory chronic lymphocytic leukemia resistant to fludarabine therapy. Haematologica 2008;93:475-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18310545.

166. Gopal AK, Davies AJ, Flinn IW, et al. Idelalisib monotherapy and durable responses in patients with relapsed or refractory small lymphocytic lymphoma (SLL) [abstract]. Blood 2015;126:Abstract 2743. Available at: http://www.bloodjournal.org/content/126/23/2743.abstract.

167. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2013;31:584-591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23270003.

168. Buhler A, Wendtner CM, Kipps TJ, et al. Lenalidomide treatment and prognostic markers in relapsed or refractory chronic lymphocytic leukemia: Data from the prospective, multicenter phase-II CLL-009 trial. Blood Cancer J 2016;6:e404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26967821.

169. Chavez JC, Piris-Villaespesa M, Dalia S, et al. Results of a phase II study of lenalidomide and rituximab for refractory/relapsed chronic lymphocytic leukemia. Leuk Res 2016;47:78-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27285853.

170. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: Final data from the phase 1/2 GAUGUIN study. Blood 2014;124:2196-2202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25143487.

171. Osterborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: Final results from a pivotal study. Haematologica 2015;100:e311-314. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25769539.

172. Wierda WG, Padmanabhan S, Chan GW, et al. Ofatumumab is active in patients with fludarabine-refractory CLL irrespective of prior rituximab: Results from the phase II international study. Blood 2011;118:5126-5129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21856867.

173. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29246803.

174. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29305552.

175. Wierda WG, Byrd JC, Davids MS, et al. Venetoclax for chronic lymphocytic leukaemia patients who progress after more than one B-cell receptor pathway inhibitor. Br J Haematol 2019;185:961-966. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30478940.

176. Mato AR, Hill BT, Lamanna N, et al. Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients. Ann Oncol 2017;28:1050-1056. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28453705.

177. van Oers MH, Kuliczkowski K, Smolej L, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): An open-label, multicentre, randomised phase 3 study. Lancet Oncol 2015;16:1370-1379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26377300.

178. Chanan-Khan AA, Zaritskey A, Egyed M, et al. Lenalidomide maintenance therapy in previously treated chronic lymphocytic leukaemia (CONTINUUM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol 2017;4:e534-e543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28958469.

179. Farooqui MZ, Valdez J, Martyr S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: A phase 2, single-arm trial. Lancet Oncol 2015;16:169-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25555420.

180. Ahn IE, Farooqui MZH, Tian X, et al. Depth and durability of response to ibrutinib in CLL: 5-year follow-up of a phase 2 study. Blood 2018;131:2357-2366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29483101.

181. Lundin J, Kimby E, Bjorkholm M, et al. Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL). Blood 2002;100:768-773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12130484.

182. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-5623. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17984186.

183. Frankfurt O, Ma S, Gordon L, et al. Phase II study of alemtuzumab-rituximab therapy in previously untreated patients with chronic lymphocytic leukemia: short- and long-term outcomes. Leuk Lymphoma 2015;56:315-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24707943.

184. Zent CS, Victoria Wang X, Ketterling RP, et al. A phase II randomized trial comparing standard and low dose rituximab combined with alemtuzumab as initial treatment of progressive chronic lymphocytic leukemia in older patients: a trial of the ECOG-ACRIN cancer research group (E1908). Am J Hematol 2016;91:308-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26662208.

185. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): A phase 2, open-label, multicentre study. Lancet Oncol 2016;17:1409-1418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27637985.

186. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for Patients With Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial. J Clin Oncol 2018;36:1973-1980. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29715056.

187. Brown JR, Flinn IW, Davids MS, et al. Clinical and Biological Indicators of Duvelisib Efficacy in CLL from the Phase 3 DUO™ Study [abstract]. Blood 2018;132:Abstract 1856. Available at: http://www.bloodjournal.org/content/132/Suppl_1/1856.abstract.

188. Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leuk Lymphoma 2007;48:2412-2417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18067017.

189. Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-1755. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20194866.

190. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood 2015;125:2497-2506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25700432.

191. Dickerson T, Wiczer T, Waller A, et al. Hypertension and Incident Cardiovascular Events Following Ibrutinib Initiation. Blood 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31582362.

192. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular Toxicities Associated With Ibrutinib. J Am Coll Cardiol 2019;74:1667-1678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31558250.

193. Hammond SP, Chen K, Pandit A, et al. Risk of hepatitis B virus reactivation in patients treated with ibrutinib. Blood 2018;131:1987-1989. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29490923.

194. Ghez D, Calleja A, Protin C, et al. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood 2018;131:1955-1959. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29437588.

195. Lampson BL, Kasar SN, Matos TR, et al. Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. Blood 2016;128:195-203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27247136.

196. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med 2016;374:311-322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26639348.

197. 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). Clinical Lymphoma Myeloma and Leukemia 2017;17:S302. Available at: http://dx.doi.org/10.1016/j.clml.2017.07.097.

198. 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. Available at:

199. Moreno C, Villamor N, Colomer D, et al. Allogeneic stem-cell transplantation may overcome the adverse prognosis of unmutated VH gene in patients with chronic lymphocytic leukemia. J Clin Oncol 2005;23:3433-3438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15809449.

200. Schetelig J, van Biezen A, Brand R, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: A retrospective european group for blood and marrow transplantation analysis. J Clin Oncol 2008;26:5094-5100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18711173.

201. Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol 2008;26:4912-4920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18794548.

202. Khouri IF, Bassett R, Poindexter N, et al. Nonmyeloablative allogeneic stem cell transplantation in relapsed/refractory chronic lymphocytic leukemia: long-term follow-up, prognostic factors, and effect of human leukocyte histocompatibility antigen subtype on outcome. Cancer 2011;117:4679-4688. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21455998.

203. Brown JR, Kim HT, Armand P, et al. Long-term follow-up of reduced-intensity allogeneic stem cell transplantation for chronic lymphocytic leukemia: prognostic model to predict outcome. Leukemia 2013;27:362-369. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22955330.

204. Dreger P, Schnaiter A, Zenz T, et al. TP53, SF3B1, and NOTCH1 mutations and outcome of allotransplantation for chronic lymphocytic leukemia: Six-year follow-up of the GCLLSG CLL3X trial. Blood 2013;121:3284-3288. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23435461.

205. Herth I, Dietrich S, Benner A, et al. The impact of allogeneic stem cell transplantation on the natural course of poor-risk chronic lymphocytic leukemia as defined by the ebmt consensus criteria: A retrospective donor versus no donor comparison. Ann Oncol 2014;25:200-206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24356631.

206. Poon ML, Fox PS, Samuels BI, et al. Allogeneic stem cell transplant in patients with chronic lymphocytic leukemia with 17p deletion: Consult-transplant versus consult- no-transplant analysis. Leuk Lymphoma 2015;56:711-715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24913509.

207. Kharfan-Dabaja MA, Kumar A, Hamadani M, et al. Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2016;22:2117-2125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27660167.

208. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912-2919. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15994282.

209. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25945807.

210. Jaglowski SM, Ruppert AS, Heerema NA, et al. Complex karyotype predicts for inferior outcomes following reduced-intensity conditioning allogeneic transplant for chronic lymphocytic leukaemia. Br J Haematol 2012;159:82-87. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22831395.

211. Tsimberidou AM, Keating MJ. Richter syndrome: Biology, incidence, and therapeutic strategies. Cancer 2005;103:216-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15578683.

212. Tsimberidou AM, O'Brien S, Kantarjian HM, et al. Hodgkin transformation of chronic lymphocytic leukemia: The M. D. Anderson cancer center experience. Cancer 2006;107:1294-1302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16902984.

213. Bockorny B, Codreanu I, Dasanu CA. Hodgkin lymphoma as Richter transformation in chronic lymphocytic leukaemia: a retrospective analysis of world literature. Br J Haematol 2012;156:50-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22017478.

214. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16710033.

215. Scandurra M, Rossi D, Deambrogi C, et al. Genomic profiling of Richter's syndrome: recurrent lesions and differences with de novo diffuse large B-cell lymphomas. Hematol Oncol 2010;28:62-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20014148.

216. Rossi D, Rasi S, Spina V, et al. Different impact of NOTCH1 and SF3B1 mutations on the risk of chronic lymphocytic leukemia transformation to Richter syndrome. Br J Haematol 2012;158:426-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22571487.

217. Villamor N, Conde L, Martinez-Trillos A, et al. NOTCH1 mutations identify a genetic subgroup of chronic lymphocytic leukemia patients with high risk of transformation and poor outcome. Leukemia 2013;27:1100-1106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23295735.

218. Chigrinova E, Rinaldi A, Kwee I, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. Blood 2013;122:2673-2682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24004666.

219. Fabbri G, Khiabanian H, Holmes AB, et al. Genetic lesions associated with chronic lymphocytic leukemia transformation to Richter syndrome. J Exp Med 2013;210:2273-2288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24127483.

220. Rossi D, Spina V, Deambrogi C, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. Blood 2011;117:3391-3401. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21266718.

221. Parikh SA, Rabe KG, Call TG, et al. Diffuse large B-cell lymphoma (Richter syndrome) in patients with chronic lymphocytic leukaemia (CLL): a cohort study of newly diagnosed patients. Br J Haematol 2013;162:774-782. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23841899.

222. Kadri S, Lee J, Fitzpatrick C, et al. Clonal evolution underlying leukemia progression and Richter transformation in patients with ibrutinib-relapsed CLL. Blood Adv 2017;1:715-727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29296715.

223. Innocenti I, Rossi D, Trape G, et al. Clinical, pathological, and biological characterization of Richter syndrome developing after ibrutinib treatment for relapsed chronic lymphocytic leukemia. Hematol Oncol 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29484684.

224. Anderson MA, Tam C, Lew TE, et al. Clinicopathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax. Blood 2017;129:3362-3370. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28473407.

225. Gine E, Martinez A, Villamor N, et al. Expanded and highly active proliferation centers identify a histological subtype of chronic lymphocytic leukemia ("accelerated" chronic lymphocytic leukemia) with aggressive clinical behavior. Haematologica 2010;95:1526-1533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20421272.

226. Bruzzi JF, Macapinlac H, Tsimberidou AM, et al. Detection of Richter's transformation of chronic lymphocytic leukemia by PET/CT. J Nucl Med 2006;47:1267-1273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16883004.

227. Noy A, Schoder H, Gonen M, et al. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). Ann Oncol 2009;20:508-512. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19139176.

228. Papajik T, Myslivecek M, Urbanova R, et al. 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography examination in patients with chronic lymphocytic leukemia may reveal Richter transformation. Leuk Lymphoma 2014;55:314-319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23656196.

229. Michallet AS, Sesques P, Rabe KG, et al. An 18F-FDG-PET maximum standardized uptake value > 10 represents a novel valid marker for discerning Richter's Syndrome. Leuk Lymphoma 2016;57:1474-1477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26402256.

230. Mato AR, Wierda WG, Davids MS, et al. Utility of PET-CT in patients with chronic lymphocytic leukemia following B-cell receptor pathway inhibitor therapy. Haematologica 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30923097.

231. Ansell SM, Li CY, Lloyd RV, Phyliky RL. Epstein-Barr virus infection in Richter's transformation. Am J Hematol 1999;60:99-104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9929100.

232. Xiao W, Chen WW, Sorbara L, et al. Hodgkin lymphoma variant of Richter transformation: morphology, Epstein-Barr virus status, clonality, and survival analysis-with comparison to Hodgkin-like lesion. Hum Pathol 2016;55:108-116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27184478.

233. Mao Z, Quintanilla-Martinez L, Raffeld M, et al. IgVH mutational status and clonality analysis of Richter's transformation: diffuse large B-cell lymphoma and Hodgkin lymphoma in association with B-cell chronic lymphocytic leukemia (B-CLL) represent 2 different pathways of disease evolution. Am J Surg Pathol 2007;31:1605-1614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17895764.

234. Langerbeins P, Busch R, Anheier N, et al. Poor efficacy and tolerability of R-CHOP in relapsed/refractory chronic lymphocytic leukemia and Richter transformation. Am J Hematol 2014;89:E239-243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25196783.

235. Rogers KA, Huang Y, Ruppert AS, 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29193006.

236. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12655528.

237. Dabaja BS, O'Brien SM, Kantarjian HM, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin (daunoXome), and dexamethasone (hyperCVXD) regimen in Richter's syndrome. Leuk Lymphoma 2001;42:329-337. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11699397.

238. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18182662.

239. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23810245.

240. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22547610.

241. Kharfan-Dabaja MA, Kumar A, Stingo FE, et al. Allogeneic Hematopoietic Cell Transplantation for Richter Syndrome: A Single-Center Experience. Clin Lymphoma Myeloma Leuk 2018;18:e35-e39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29126867.

242. 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. Available at: http://www.bloodjournal.org/content/132/Suppl_1/296.abstract.

243. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30642819.

244. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28424162.

245. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30028000.

246. Tadmor T, Shvidel L, Goldschmidt N, et al. Hodgkin's variant of Richter transformation in chronic lymphocytic leukemia; a retrospective study from the Israeli CLL study group. Anticancer Res 2014;34:785-790. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24511013.

247. Parikh SA, Habermann TM, Chaffee KG, et al. Hodgkin transformation of chronic lymphocytic leukemia: Incidence, outcomes, and comparison to de novo Hodgkin lymphoma. Am J Hematol 2015;90:334-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25581025.

248. Mauro FR, Galieni P, Tedeschi A, et al. Factors predicting survival in chronic lymphocytic leukemia patients developing Richter syndrome transformation into Hodgkin lymphoma. Am J Hematol 2017;92:529-535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28295527.

249. Tsai HT, Caporaso NE, Kyle RA, et al. Evidence of serum immunoglobulin abnormalities up to 9.8 years before diagnosis of chronic lymphocytic leukemia: A prospective study. Blood 2009;114:4928-4932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19828698.

250. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: Pathogenesis, spectrum of infection, preventive approaches. Best Pract Res Clin Haematol 2010;23:145-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20620978.

251. Perkins JG, Flynn JM, Howard RS, Byrd JC. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma. Cancer 2002;94:2033-2039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11932906.

252. Chapel H, Dicato M, Gamm H, et al. Immunoglobulin replacement in patients with chronic lymphocytic leukaemia: A comparison of two dose regimes. Br J Haematol 1994;88:209-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7803248.

253. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative group for the study of immunoglobulin in chronic lymphocytic leukemia. N Engl J Med 1988;319:902-907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2901668.

254. Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol 1995;17:75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7621634.

255. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica 1996;81:121-126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8641639.

256. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: Systematic review and meta-analysis. Leukemia & Lymphoma 2009;50:764-772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19330654.

257. Kim DK, Bridges CB, Harriman KH, Advisory Committee on Immunization P. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United states, 2015*. Ann Intern Med 2015;162:214-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25643306.

258. Sinisalo M, Vilpo J, Itala M, et al. Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. Vaccine 2007;26:82-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18053620.

259. Sinisalo M, Aittoniemi J, Kayhty H, Vilpo J. Vaccination against infections in chronic lymphocytic leukemia. Leuk Lymphoma 2003;44:649-652. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12769342.

260. Yeo W, Chan PK, Zhong S, et al. Frequency of Hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: A prospective study of 626 patients with identification of risk factors. J Med Virol 2000;62:299-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11055239.

261. Lau GK. Hepatitis B reactivation after chemotherapy: Two decades of clinical research. Hepatol Int 2008;2:152-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19669300.

262. FDA drug safety communication: Boxed warning and new recommendations to decrease risk of Hepatitis B reactivation with the immune-suppressing and anti-cancer drugs arzerra (ofatumumab) and rituxan (rituximab); September 25, 2013. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM369436.pdf.

263. Arnold DM, Crowther MA, Meyer RM, et al. Misleading Hepatitis B test results due to intravenous immunoglobulin administration: Implications for a clinical trial of rituximab in immune thrombocytopenia. Transfusion 2010;50:2577-2581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20576011.

264. Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated Hepatitis B virus reactivation in patients with lymphoma and resolved Hepatitis B. J Clin Oncol 2013;31:2765-2772. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23775967.

265. Kim SJ, Hsu C, Song YQ, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: Analysis from the asia lymphoma study group. Eur J Cancer 2013;49:3486-3496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23910494.

266. Liang R. How I treat and monitor viral Hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 2009;113:3147-3153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19144986.

267. O'Brien SM, Keating MJ, Mocarski ES. Updated guidelines on the management of cytomegalovirus reactivation in patients with chronic lymphocytic leukemia treated with alemtuzumab. Clin Lymphoma Myeloma 2006;7:125-130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17026823.

268. Laurenti L, Piccioni P, Cattani P, et al. Cytomegalovirus reactivation during alemtuzumab therapy for chronic lymphocytic leukemia: Incidence and treatment with oral ganciclovir. Haematologica 2004;89:1248-1252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15477211.

269. Visani G, Mele A, Guiducci B, et al. An observational study of once weekly intravenous ganciclovir as cmv prophylaxis in heavily pre-treated chronic lymphocytic leukemia patients receiving subcutaneous alemtuzumab. Leuk Lymphoma 2006;47:2542-2546. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17169798.

270. Dearden C. Disease-specific complications of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2008;2008:450-456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19074125.

271. Zent CS, Kay NE. Autoimmune complications in chronic lymphocytic leukaemia (CLL). Best Pract Res Clin Haematol 2010;23:47-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20620970.

272. Borthakur G, O'Brien S, Wierda WG, et al. Immune anaemias in patients with chronic lymphocytic leukaemia treated with fludarabine, cyclophosphamide and rituximab – incidence and predictors. British Journal of Haematology 2007;136:800-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17341265.

273. Barcellini W, Capalbo S, Agostinelli R, et al. Relationship between autoimmune phenomena and disease stage and therapy in B-cell chronic lymphocytic leukemia. Haematologica 2006;91:1689-1692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17145607.

274. Zanotti R, Frattini F, Ghia P, et al. ZAP-70 expression is associated with increased risk of autoimmune cytopenias in CLL patients. Am J Hematol 2010;85:494-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20575031.

275. Moreno C, Hodgson K, Ferrer G, et al. Autoimmune cytopenias in chronic lymphocytic leukemia: Prevalence, clinical associations, and prognostic significance. Blood 2010;116:4771-4776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20736453.

276. Dearden C, Wade R, Else M, et al. The prognostic significance of a positive direct antiglobulin test in chronic lymphocytic leukemia: A beneficial effect of the combination of fludarabine and cyclophosphamide on the incidence of hemolytic anemia. Blood 2008;111:1820-1826. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18055869.

277. Visco C, Ruggeri M, Laura Evangelista M, et al. Impact of immune thrombocytopenia on the clinical course of chronic lymphocytic leukemia. Blood 2008;111:1110-1116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17986663.

278. Cortes J, O'Brien S, Loscertales J, et al. Cyclosporin a for the treatment of cytopenia associated with chronic lymphocytic leukemia. Cancer 2001;92:2016-2022. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11596014.

279. Hegde UP, Wilson WH, White T, Cheson BD. Rituximab treatment of refractory fludarabine-associated immune thrombocytopenia in chronic lymphocytic leukemia. Blood 2002;100:2260-2262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12200396.

280. Ghazal H. Successful treatment of pure red cell aplasia with rituximab in patients with chronic lymphocytic leukemia. Blood 2002;99:1092-1094. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11807020.

281. Gupta N, Kavuru S, Patel D, et al. Rituximab-based chemotherapy for steroid-refractory autoimmune hemolytic anemia of chronic lymphocytic leukemia. Leukemia 2002;16:2092-2095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12357362.

282. Shanafelt TD, Madueme HL, Wolf RC, Tefferi A. Rituximab for immune cytopenia in adults: Idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and evans syndrome. Mayo Clin Proc 2003;78:1340-1346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14601692.

283. D'Arena G, Laurenti L, Capalbo S, et al. Rituximab therapy for chronic lymphocytic leukemia-associated autoimmune hemolytic anemia. Am J Hematol 2006;81:598-602. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16823816.

284. Berentsen S. Rituximab for the treatment of autoimmune cytopenias. Haematologica 2007;92:1589-1596. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18055980.

285. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: Results of a prospective multicenter phase 2 study. Blood 2008;112:925-926. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18463354.

286. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: A double-blind randomised controlled trial. Lancet 2008;371:395-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18242413.

287. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. N Engl J Med 2010;363:1889-1899. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21067381.

288. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007;357:2237-2247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18046028.

289. Bussel JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009;113:2161-2171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18981291.

290. Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111:5291-5297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18334676.

291. Chen CI, Paul H, Wang T, et al. Long-term follow-up of a phase 2 trial of single agent lenalidomide in previously untreated patients with chronic lymphocytic leukaemia. Br J Haematol 2014;165:731-733. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24611934.

292. James DF, Werner L, Brown JR, et al. Lenalidomide and rituximab for the initial treatment of patients with chronic lymphocytic leukemia: A multicenter clinical-translational study from the chronic lymphocytic leukemia research consortium. J Clin Oncol 2014;32:2067-2073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24868031.

293. Andritsos LA, Johnson AJ, Lozanski G, et al. Higher doses of lenalidomide are associated with unacceptable toxicity including life-threatening tumor flare in patients with chronic lymphocytic leukemia. J Clin Oncol 2008;26:2519-2525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18427150.

294. Wendtner CM, Hallek M, Fraser GA, et al. Safety and efficacy of different lenalidomide starting doses in patients with relapsed or refractory chronic lymphocytic leukemia: Results of an international multicenter double-blinded randomized phase II trial. Leuk Lymphoma 2016;57:1291-1299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26763349.

295. Aue G, Nelson Lozier J, Tian X, et al. Inflammation, TNFalpha and endothelial dysfunction link lenalidomide to venous thrombosis in chronic lymphocytic leukemia. Am J Hematol 2011;86:835-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21812019.

296. Castillo JJ, Kanan S, Meid K, et al. Rituximab intolerance in patients with Waldenstrom macroglobulinaemia. Br J Haematol 2016;174:645-648. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26523929.

297. Chen LY, Shah R, Cwynarski K, et al. Ofatumumab is a feasible alternative anti-CD20 therapy in patients intolerant of rituximab. Br J Haematol 2019;184:462-465. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29363752.

298. Assouline S, Buccheri V, Delmer A, et al. Pharmacokinetics, safety, and efficacy of subcutaneous versus intravenous rituximab plus chemotherapy as treatment for chronic lymphocytic leukaemia (SAWYER): a phase 1b, open-label, randomised controlled non-inferiority trial. Lancet Haematol 2016;3:e128-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26947201.