National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

Version 1.2023 — August 30, 2022

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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NCCN Guidelines Version 1.2023
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

Updates in Version 1.2023 of the NCCN Guidelines for CLL/SLL from Version 3.2022 include:

Global
- References were updated throughout the guidelines.
- Ofatumumab (monotherapy or in combination regimens) removed due to limited clinical use and availability

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CSLL-1
- Diagnosis, Essential
  - 2nd bullet, 3rd sub-bullet revised: …CD10, *CD200*; if flow is used to establish diagnosis,…~~CD200 positivity may distinguish CLL from mantle cell lymphoma (MCL), which is usually CD200-~~.
  - 3rd bullet, 1st sub-bullet revised: …cyclin D1, *LEF1, SOX11*. ~~LEF1 expression may distinguish CLL from MCL, which is usually LEF1-~~.
- Footnotes
  - Footnote b revised by adding: CD200 positivity may distinguish CLL from mantle cell lymphoma (MCL), which is usually CD200-.
  - Footnote d added: LEF1 and SOX11 may be helpful in suspected cases of mantle cell lymphoma that are cyclin D1-negative.

CSLL-2
- Workup
  - Essential, 5th bullet; LDH was moved from Useful Under Certain Circumstances and added as "including lactate dehydrogenase (LDH)."
  - Useful, 10th bullet revised: Discussion of fertility ~~issues and sperm banking~~ *preservation*. Corresponding footnote j added: Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation. (Also for HT-2)

CSLL-3
- Footnote n revised: Absolute lymphocyte count alone is not an indication for treatment ~~since leukostasis~~ *in the absence of leukostasis, which* is rarely seen in CLL.

CSLL-4
- CLL/SLL without del(17p)/TP53 mutation
  - Algorithm was extensively revised to include sequencing of therapy for relapsed or refractory disease; second- and third-line therapy options are now based on type of therapy received for first-line therapy and response to first-line therapy (CSLL-4A and CSLL-4B).

CSLL-4A
- Footnotes
  - Footnote s added: If progression with indication for subsequent therapy: Re-evaluate with FISH for del(17p)/TP53 mutation status and CpG-stimulated karyotype, prior to initiation of subsequent therapy. (Also for CSLL-4B)
  - Footnote t revised: …*including if poor compliance is considered as a possible cause.* BTK and PLCG2 mutation status alone is not an indication to change treatment. *Alternative covalent BTKi could be considered in the setting of poor compliance or intolerance but is not a reasonable treatment option for patients with mutation in either BTK or PLCG2.* (Also for CSLL-4B and CSLL-5)
  - Footnote u added: Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation. If histologic transformation or histologic progression of CLL/SLL, see HT-1. (Also for CSLL-4B)
  - Footnote v added: In patients with disease responding to therapy: Continue the same BTKi until progression and/or intolerance. If treated with venetoclax-based fixed duration treatment, observe until relapse with indications for retreatment. (Also for CSLL-4B)
  - Footnote removed: Given incurability with conventional therapy, consider including clinical trial as first-line therapy.

CSLL-4B
- Footnote x added: CIT or immunotherapy is not an option for patients who have received these regimens for first-line therapy.

Continued

Updates in Version 1.2023 of the NCCN Guidelines for CLL/SLL from Version 3.2022 include:

CSLL-5
- CLL/SLL with del(17p)/TP53 mutation
  - Additional therapy revised: Continue treatment with ~~BCR pathway~~ *same BTKi* until progression *and/or intolerance* ~~or Observation, if treated with targeted therapy with fixed duration treatment until indication for retreatment as listed on CSLL-3~~ *Observe until relapse with indications for treatment if treated with venetoclax + anti-CD20 mAb or other recommended immunotherapy-based regimens*
  - Second-line and subsequent therapy, 2nd option revised: Consider allogeneic HCT, if without significant comorbidities in patients with ~~CLL/SLL refractory to small-molecule inhibitor therapy~~ *relapsed or refractory disease after prior therapy with BTKi- and venetoclax-based regimen*
  - Footnote z added: Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation.

CSLL-A
- Prognostic information for CLL/SLL
  - Footnote a revised: …in patients who received *chemoimmunotherapy-based* treatment. *The significance of these prognostic variables in patients treated with targeted* therapy are less well-defined.

CSLL-B 1 of 2
- Rai system, Stage 0 description revised: ...B cells and*/or* >40% lymphocytes in the bone marrow

CSLL-C 1 of 5
- Anti-infective Prophylaxis, 2nd bullet revised: See CSLL-F for recommended ~~antimicrobial~~ *antiviral and PJP prophylaxis* for *patients receiving* small-molecule inhibitor therapies.
- Treatment and Viral Reactivation, 1st bullet revised: testing for all patients receiving ~~anti-CD20 antibody~~ therapy

CSLL-C 2 of 5
- Treatment of TLS, First-line and at retreatment for hyperuricemia revised:
  - *Glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to use of rasburicase. Rasburicase is contraindicated in patients with a history consistent with G6PD. In these patients, rasburicase should be substituted with allopurinol.*

  Low Risk Disease: Allopurinol or febuxostat if intolerant to allopurinol beginning 2–3 days prior to chemoimmunotherapy and continued for 10–14 days

  Intermediate Risk Disease: Stage I/II and LDH <2X ULN: Allopurinol or febuxostat

  OR

  Rasburicase if renal dysfunction and uric acid, potassium, and/or phosphate >ULN

  High Risk Disease: Stage III/IV and/or LDH ≥2X ULN: Rasburicase

CSLL-C 3 of 5
- Autoimmune Cytopenias, 4th sub-bullet revised by adding: …or BTKi-based therapy for steroid-refractory or recurrent AIHA.

CSLL-C 5 of 5
- Vaccination,
  - 3rd bullet updated: Pneumococcal vaccine updated:
    - ◊ Pneumococcal polysaccharide vaccine (PPSV23) every 5 years *or to maintain protective serologic antibody levels based on serologic testing.*
    - ◊ *The pneumococcal conjugate vaccine (PCV20) should be administered...Therefore, PCV7 and PCV13 should not be given with MenACWY-D but can be given with MenACWY-CRM.*
  - COVID-19, 3rd sub-bullet added: Consider COVID prophylaxis with tixagevimab and cilgavimab for all patients with CLL/SLL.

Continued

Updates in Version 1.2023 of the NCCN Guidelines for CLL/SLL from Version 3.2022 include:

CSLL-D 1 of 6

- CLL/SLL without del(17p)/TP53 mutation, First-line therapy
  - Regimens reorganized by removing qualifiers:
    - ◊ Patients age ≥65 y OR Patients age <65 years with significant comorbidities (creatinine clearance [CrCl] <70 mL/ min).
    - ◊ Patients age <65 y with significant comorbidities.
  - Ibrutinib was moved from Preferred regimens to Other recommended regimens. Corresponding footnote h added: The panel consensus to list ibrutinib under "other recommended regimens" is based on the toxicity profile. A baseline assessment of cardiac function should be done prior to initiation of ibrutinib. In patients with no intolerance, ibrutinib can be continued until disease progression.
  - Preferred regimens
    - ◊ Venetoclax + obinutuzumab was changed from a category 2A to category 1 recommendation for patients age < 65 y without significant comorbidities).
    - ◊ Zanubrutinib was changed from a category 2A to category 1 recommendation.
  - Other recommended regimens
    - ◊ Added: Ibrutinib + venetoclax as a category 2B recommendation
    - ◊ Removed the following regimens
      - – Chlorambucil (category 3)
      - – Rituximab (category 3)
      - – FR (fludarabine + rituximab) (category 3)
  - Useful in certain circumstances
    - ◊ FCR (fludarabine, cyclophosphamide, rituximab) moved under Useful in certain circumstances with the qualifier: consider for IGHV-mutated CLL in patients age <65 y without significant comorbidities.

CSLL-D 2 of 6

- CLL/SLL without del(17p)/TP53 mutation, Second-line and Subsequent Therapy
  - Regimens were reorganized as follows:
    - ◊ Second-line therapy or third-line therapy
    - ◊ Therapy for relapsed or refractory disease after prior BTKi- and venetoclax-based regimens
  - Second-line therapy or third-line therapy
    - ◊ Ibrutinib was moved from Preferred regimens to Other recommended regimens. Corresponding footnote h added: The panel consensus to list ibrutinib under "other recommended regimens" is based on the toxicity profile. A baseline assessment of cardiac function should be done prior to initiation of ibrutinib. In patients with no intolerance, ibrutinib can be continued until disease progression.
    - ◊ Added: Retreatment with venetoclax + obinutuzumab as a category 2A recommendation under useful in certain circumstances (for relapse after a period of remission if previously used as first line therapy)
    - ◊ Removed the following regimens
      - – Chlorambucil + rituximab (category 2A)
      - – Alemtuzumab ± rituximab (category 3)
      - – Bendamustine, rituximab + ibrutinib (category 3)
      - – Dose-dense rituximab (category 3)

Continued

Updates in Version 1.2023 of the NCCN Guidelines for CLL/SLL from Version 3.2022 include:

CSLL-D 3 of 6
- CLL/SLL with del(17p)/TP53 mutation, Second-line and Subsequent Therapy
  - First-line therapy and Second-line and subsequent therapy
    - ◊ Ibrutinib was moved from Preferred regimens to Other recommended regimens. Corresponding footnote h added: The panel consensus to list ibrutinib under "other recommended regimens" is based on the toxicity profile. A baseline assessment of cardiac function should be done prior to initiation of ibrutinib. In patients with no intolerance, ibrutinib can be continued until disease progression.
    - ◊ Other recommended regimens, added: Ibrutinib + venetoclax as a category 2B recommendation
  - Second-line and subsequent therapy, Other recommended regimens
    - ◊ Ofatumumab was removed due to limited clinical use and availability.

CSLL-E 1 of 2
- Response definitions after treatment for CLL/SLL
  - Lymph nodes, CR was revised: None ≥1.5 cm *in longest dimension*

CSLL-F 1 of 3
- Acalabrutinib, Drug interactions: Miscellaneous revised: Avoid co-administration *of capsule formulation* with proton pump inhibitors and stagger dosing with H2-receptor antagonists and antacids; triazoles and fluoroquinolones increase drug levels.
- Footnote a revised by adding: It is safe to overlap with venetoclax while on BTKi.

CSLL-F 2 of 3
- Idelalisib
  - Most common adverse events revised by removing: abdominal pain (28%)
  - Hepatoxicity revised by removing: Discontinue if ALT/AST >20 x ULN

CSLL-F 3 of 3
- Venetoclax, drug interactions with CYP3A inhibitors updated.

ABBR-1
- New section added: Abbreviations

DIAGNOSIS[a]
ESSENTIAL:
- **Hematopathology review of peripheral blood smear and all slides with at least one paraffin block representative of the tumor, if the diagnosis was made on a lymph node or bone marrow biopsy.**
- **Flow cytometry of blood is adequate for the diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (biopsy is 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, CD200; if flow cytometry is used to establish diagnosis, also include cytospin for cyclin D1 or fluorescence in situ hybridization (FISH) for t(11;14); t(11q;v).**
  - **SLL diagnosis requires presence of lymphadenopathy and/or splenomegaly with monoclonal B lymphocytes ≤5 x 10^9/L in peripheral blood**
  - **SLL diagnosis should be confirmed by histopathology evaluation of lymph node biopsy**
- **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 fine-needle aspiration (FNA) or core needle biopsy alone is not generally suitable for the initial diagnosis of CLL/SLL. In certain circumstances, when a lymph node is not easily accessible for excisional or incisional biopsy, a combination of core 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, SOX11.[d]**
- **Absolute monoclonal B lymphocyte count[c]**

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:[e]
- **FISH to detect: +12; del(11q); del(13q); del(17p)**
- ***TP53* sequencing**
- **CpG-stimulated metaphase karyotype for complex karyotype (CK)**
- **Molecular analysis to detect: Immunoglobulin heavy chain variable region gene (IGHV) mutation status[f]**

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] 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+ or CD23- or dim, and some MCL may be CD23+; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases, especially for those with an atypical immunophenotype (ie, CD23 dim or negative, CD20 bright, sIg bright). CD200 positivity may distinguish CLL from mantle cell lymphoma (MCL), which is usually CD200-.

[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 the same phenotype may be seen in reactive lymph nodes; therefore, diagnosis of SLL should only be made when effacement of lymph node architecture is seen.

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

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

[f] IGHV mutation status is preferred over flow cytometry. 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.

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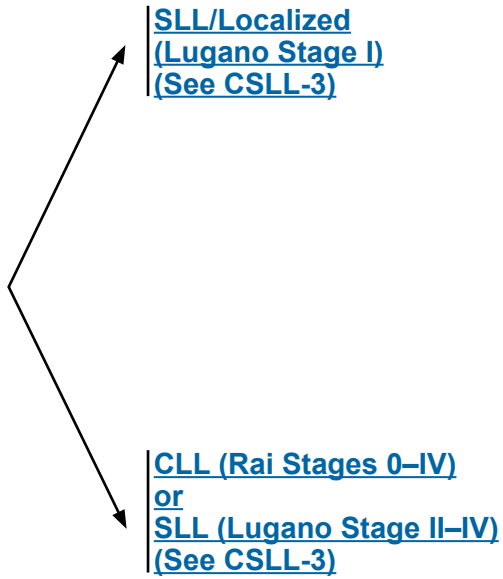
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

WORKUP

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

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- **Quantitative immunoglobulins**
- **Reticulocyte count, haptoglobin, and direct antiglobulin test (Coombs)**
- **Chest/abdominal/pelvic CT with contrast of diagnostic quality, if clinically indicated[g]**
- **Beta-2-microglobulin**
- **Uric acid**
- **Unilateral bone marrow aspirate + biopsy[h]**
- **Hepatitis B[i] and C testing if treatment is contemplated**
- **Multigated acquisition (MUGA) scan/echocardiogram if anthracycline-based regimen is indicated**
- **Pregnancy testing in females of childbearing age if systemic therapy or RT is planned**
- **Discussion of fertility preservation[j]**
- **PET/CT scan to direct nodal biopsy, if histologic transformation is suspected. See HT-1.**



[g] 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.
[h] May be informative for the diagnosis of immune-mediated or disease-related cytopenias.
[i] 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 a gastroenterologist.
[j] Fertility preservation options include: sperm banking, semen cryopreservation, in vitro fertilization (IVF), or ovarian tissue or oocyte cryopreservation.

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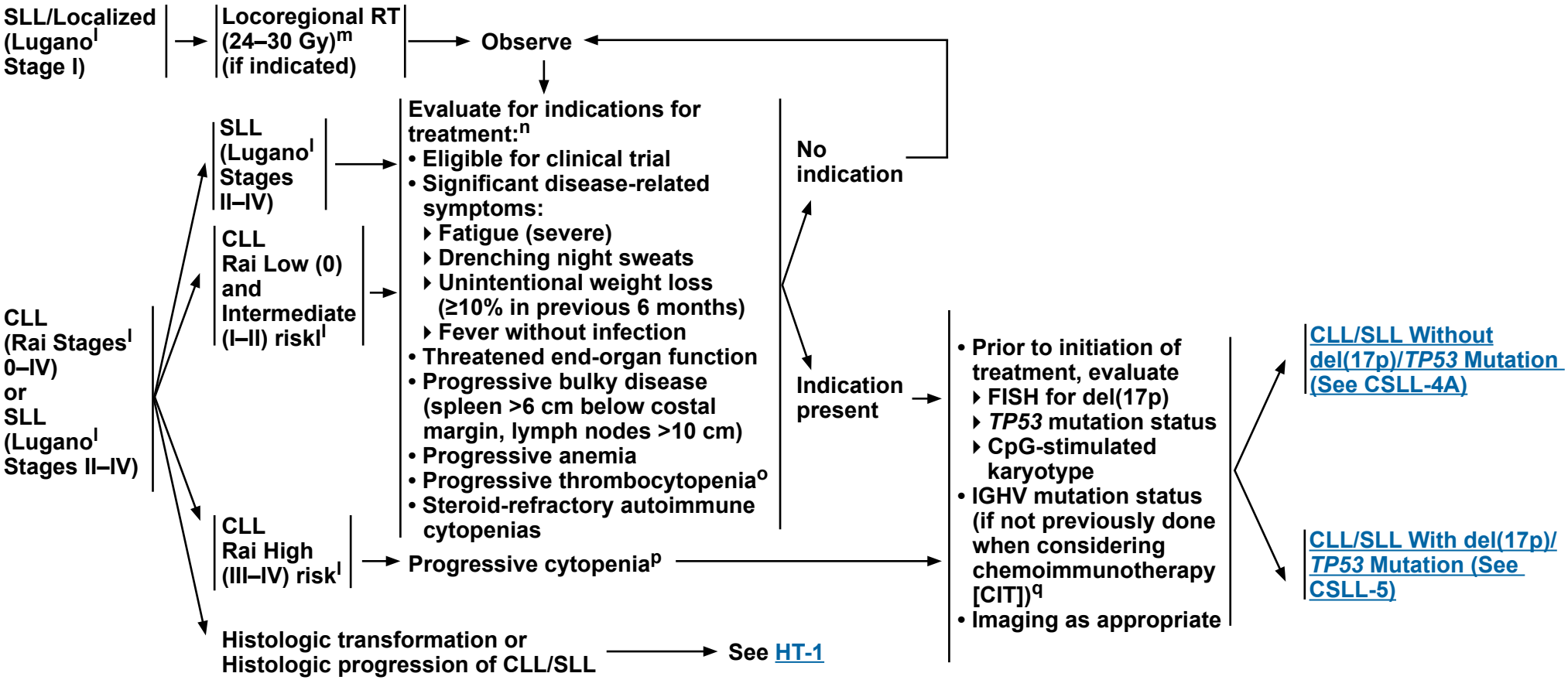
PRESENTATION[k]



[k] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[l] See Rai and Binet Classification Systems (CSLL-B 1 of 2) and Lugano Modification of Ann Arbor Staging System (CSLL-B 2 of 2).
[m] 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.
[n] Absolute lymphocyte count alone is not an indication for treatment in the absence of leukostasis, which is rarely seen in CLL.
[o] Platelet counts >100,000 cells/mm^3 are typically not associated with clinical risk.
[p] 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.
[q] IGHV mutation status does not change over time and analysis does not need to be repeated if previously done prior to initiation of treatment.

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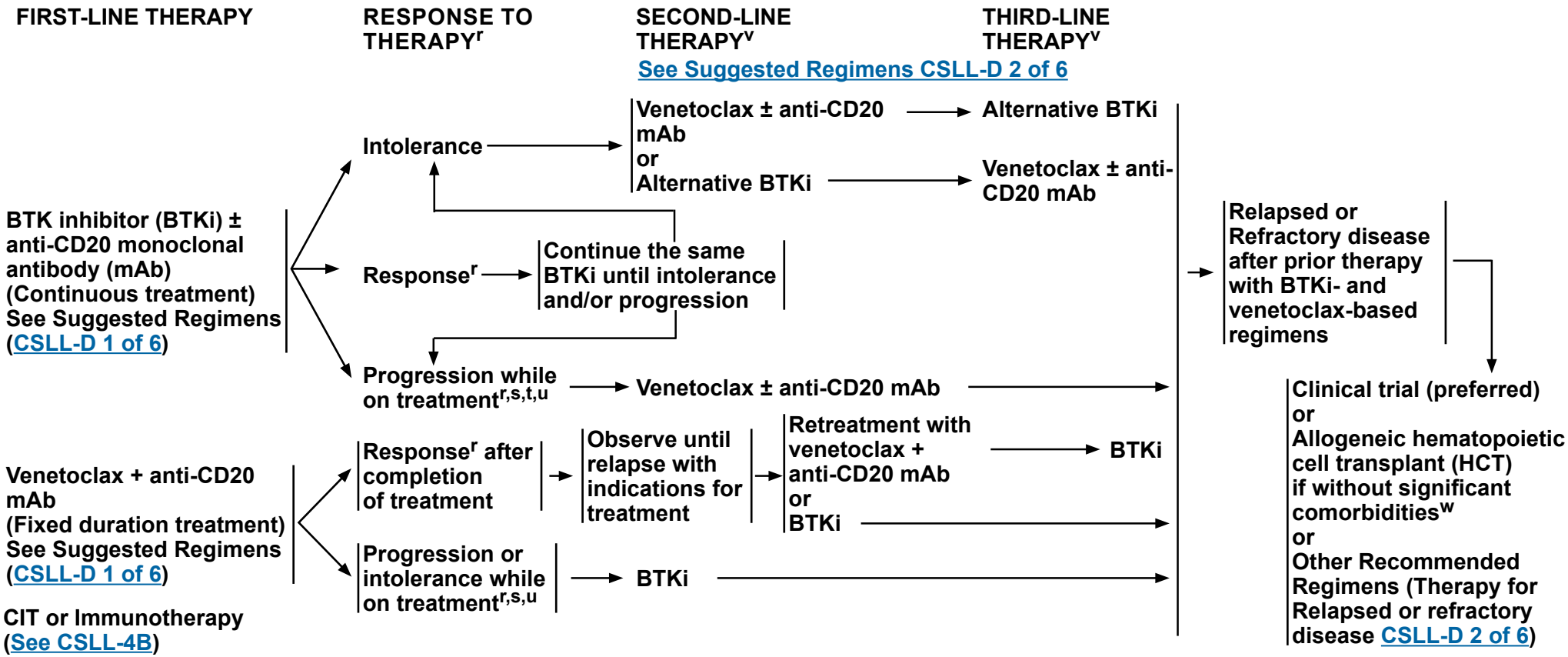
CLL/SLL WITHOUT DEL(17p)/*TP53* MUTATION[k]



[k] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[r] See Response Definition after Treatment for CLL/SLL (CSLL-E).
[s] If progression with indication for subsequent therapy: Re-evaluate with FISH for del(17p)/*TP53* mutation status and CpG-stimulated karyotype, prior to initiation of subsequent therapy.
[t] Testing for *BTK* and *PLCG2* mutations may be useful in patients with disease progression or no response while on BTKi therapy including if poor compliance is considered as a possible cause. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment. Alternative covalent BTKi could be considered in the setting of poor compliance or intolerance but is not a reasonable treatment option for patients with mutation in either *BTK* or *PLCG2*.
[u] Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation. If histologic transformation or histologic progression of CLL/SLL, see HT-1.
[v] In patients with disease responding to therapy: Continue the same BTKi until progression and/or intolerance. If treated with venetoclax-based fixed duration treatment, observe until relapse with indications for retreatment.
[w] ElSawy M, et al. Br J Haematol 2015;170:574-583.

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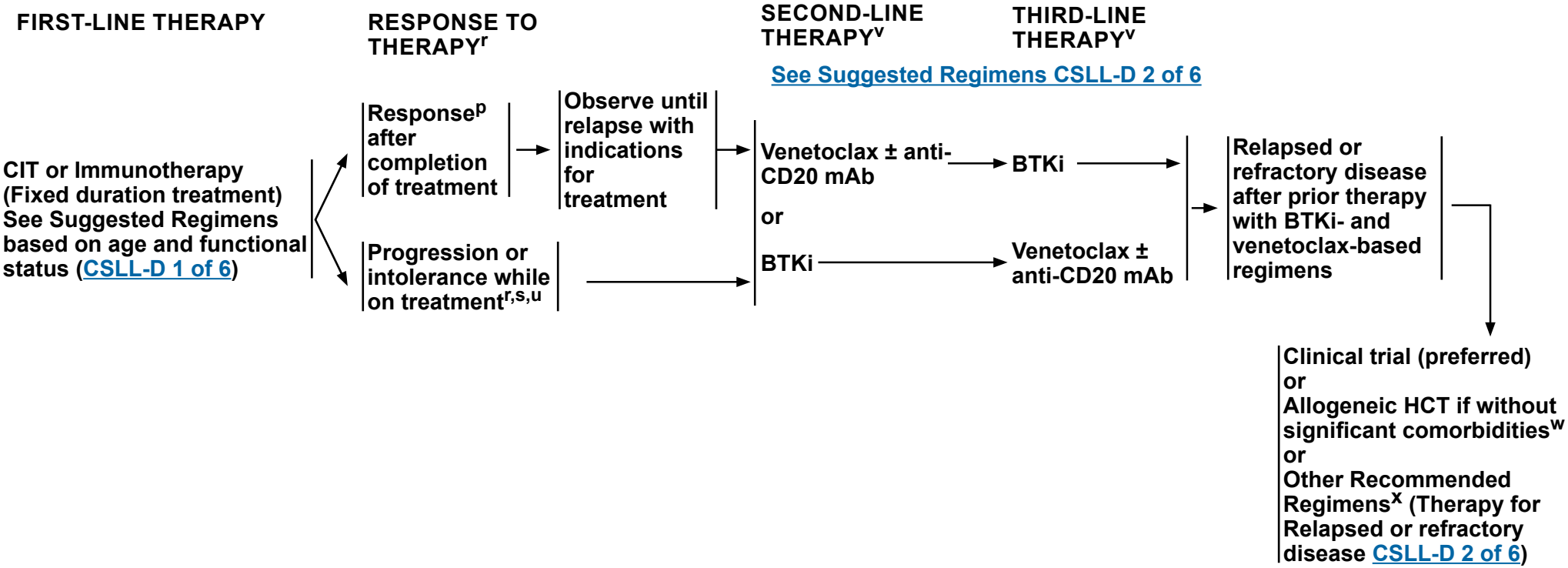
CLL/SLL WITHOUT DEL(17p)/*TP53* MUTATION[k]



[k] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[r] See Response Definition after Treatment for CLL/SLL (CSLL-E).
[s] If progression with indication for subsequent therapy: Re-evaluate with FISH for del(17p)/*TP53* mutation status and CpG-stimulated karyotype, prior to initiation of subsequent therapy
[u] Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation. If histologic transformation or histologic progression of CLL/SLL, see HT-1.
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[w] ElSawy M, et al. Br J Haematol 2015;170:574-583.
[x] CIT or immunotherapy is not an option for patients who have received these regimens for first-line therapy.

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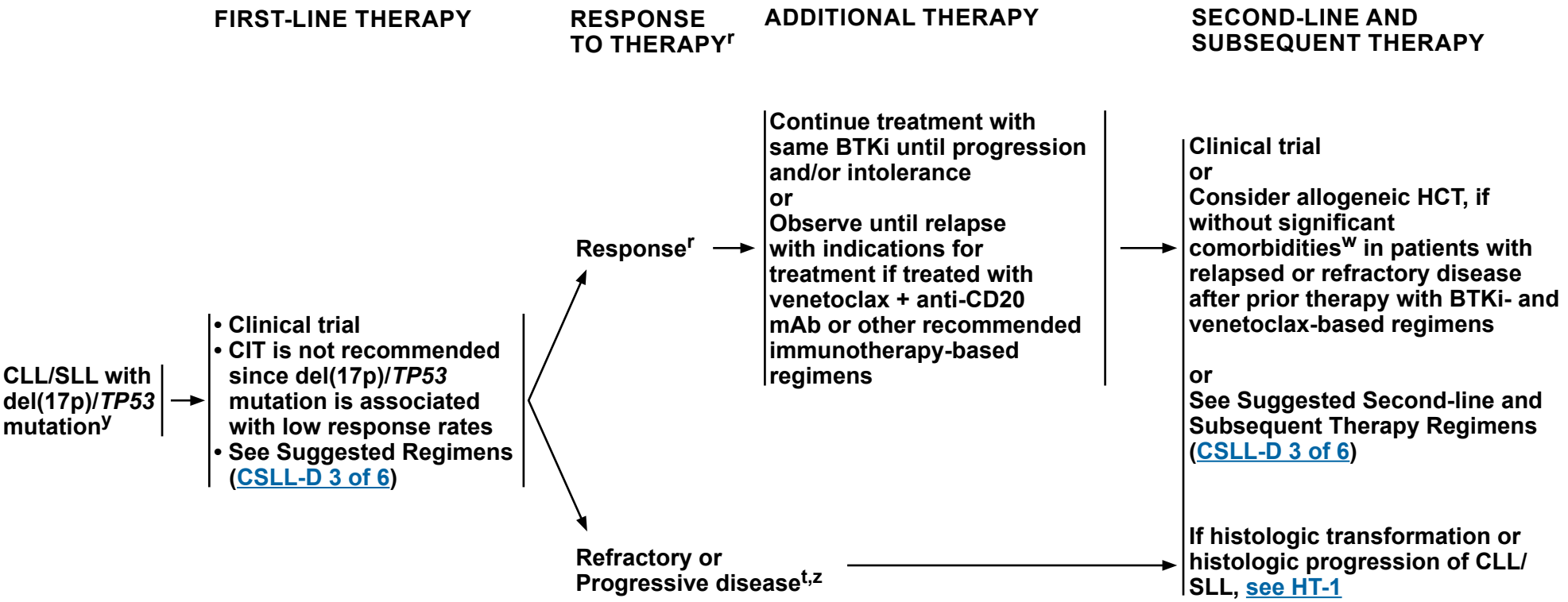
CLL/SLL WITH DEL(17p)/*TP53* MUTATION[k]



[k] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[r] See Response Definition After Treatment for CLL/SLL (CSLL-E).
[t] Testing for *BTK* and *PLCG2* mutations may be useful in patients with disease progression or no response while on BTKi therapy including if poor compliance is considered as a possible cause. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment. Alternative covalent BTKi could be considered in the setting of poor compliance or intolerance but is not a reasonable treatment option for patients with mutation in either *BTK* or *PLCG2*.
[w] ElSawy M, et al. Br J Haematol 2015;170:574-583.
[y] CPG-stimulated karyotype is useful to identify high-risk patients, particularly for patients receiving BTKi therapy.
[z] Consider the possibility of histologic transformation in patients with progressive disease. Biopsy is recommended to confirm histologic transformation.

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PROGNOSTIC INFORMATION FOR CLL/SLL[a]

Method of Detection	Prognostic Variable	Risk Category
Interphase cytogenetics (FISH)[b]	del(17p)	Unfavorable
	del(11q)	Unfavorable
	+12	Intermediate
	Normal	Intermediate
	del(13q) (as a sole abnormality)	Favorable
DNA sequencing[c]	*TP53*	Wild-type: Favorable Mutated: Unfavorable
	IGHV	>2% mutation: Favorable ≤2% mutation: Unfavorable
CpG-stimulated metaphase karyotype	CK[d] (≥3 unrelated clonal chromosome abnormalities in more than one cell on karyotype)	Unfavorable

[a] This table provides useful prognostic information for survival and time to progression in patients who received chemoimmunotherapy-based treatment. The significance of these prognostic variables in patients treated with targeted therapy are less well-defined.
[b] 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.
[c] IGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated. *TP53* mutation status also provides additional prognostic information to FISH.
[d] CK is based on results of metaphase karyotyping of CpG-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/or >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0–I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV[c]	Stage 0–III with platelets <100,000/mm^3	High

Binet System[b]

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

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

Continued

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

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

[d] Extent of disease is determined by 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.

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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
- See CSLL-F for recommended antiviral and PJP prophylaxis for patients receiving small-molecule inhibitor therapies.
- 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

HBV:

- Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (HBcAb) testing for all patients receiving therapy
  - Quantitative hepatitis B viral load by quantitative RT-PCR (qPCR) and surface antibody only if one of the screening tests is positive
- Patients receiving intravenous immunoglobulin (IVIG) may be HBcAb-positive as a consequence of IVIG therapy.
- Prophylactic antiviral therapy with entecavir is recommended for any patient who is HBsAg-positive and receiving treatment. If there is active disease (qPCR+), it is considered treatment/management and not prophylactic therapy. In cases of HBcAb positivity, prophylactic antiviral therapy is preferred; however, if there is a concurrent high-level hepatitis B surface antibody, these patients may be monitored with serial hepatitis B viral load.
  - Entecavir is preferred (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 qPCR 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 qPCR becomes positive, consult hepatologist and discontinue anti-CD20 antibody therapy.
  - Maintain prophylaxis up to 12 months after oncologic treatment ends.
    - ◊ Consult with hepatologist for duration of therapy in patient with active HBV.

Hepatitis C virus (HCV):

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

CMV reactivation in previously infected (seropositive) patients:

- Clinicians must be aware of the high risk of CMV reactivation in patients receiving phosphoinositide 3-kinase (PI3K) inhibitors or alemtuzumab. The current recommendations for appropriate screening are controversial. CMV viremia should be measured by PCR at least every 4 weeks. Some clinicians use ganciclovir (oral or IV) pre-emptively if viremia is present; others use ganciclovir only if viral load is rising. Consultation with an infectious disease expert may be necessary.

John Cunningham (JC) virus:

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

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Tumor Lysis Syndrome (TLS)

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

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

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

- Treatment of TLS:
  - TLS is best managed if anticipated and treatment is started prior to chemotherapy.
  - Centerpiece of treatment includes:
    - ◊ Rigorous hydration
    - ◊ Management of hyperuricemia
    - ◊ Frequent monitoring of electrolytes and aggressive correction (essential)
  - First-line and at retreatment for hyperuricemia
    - ◊ Glucose-6-phosphate dehydrogenase (G6PD) testing is required prior to use of rasburicase. Rasburicase is contraindicated in patients with a history consistent with G6PD. In these patients, rasburicase should be substituted with allopurinol.
    - ◊ Low Risk Disease: Allopurinol or febuxostat beginning 2–3 days prior to chemoimmunotherapy and continued for 10–14 days
    - ◊ Intermediate Risk Disease (Stage I/II and LDH <2X ULN): Allopurinol or febuxostat OR Rasburicase if renal dysfunction and uric acid, potassium, and/or phosphate >ULN
    - ◊ High Risk Disease (Stage III/IV and/or LDH ≥2X ULN): Rasburicase
  - Rasburicase (doses of 3–6 mg are usually effective.[a] One dose of rasburicase is frequently adequate. Re-dosing should be individualized) is indicated for patients with any of the following risk factors:
    - ◊ Urgent need to initiate therapy in a patient with bulky disease
    - ◊ Situations where adequate hydration may be difficult or impossible
    - ◊ Acute renal failure
  - If TLS is untreated, its progression may cause acute kidney failure, cardiac arrhythmias, seizures, loss of muscle control, and death.

[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 (Coombs).
  - AIHA that develops in the setting of treatment with fludarabine: Stop, treat, and avoid subsequent fludarabine.
- Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets.
- Pure red cell aplasia (PRCA): Consider bone marrow evaluation and testing for parvovirus B19, herpes virus, and drug effects.
- Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP), or BTKi-based therapy for steroid-refractory or recurrent AIHA.

Blood Product Support

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

Cancer Screening

- 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-melanoma skin cancers.
  - Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) were 7 times and 14 times more likely to recur in patients with CLL/SLL than in controls (Mehrany K, et al. Dermatol Surg 2005;31:38-42; Mehrany K, et al. Arch Dermatol 2004;140:985-988).
  - Patients with CLL/SLL are more likely to die from SCC or have metastatic SCC than those without CLL/SLL (Mehrany, K et al. J Am Acad Dermatol 2005;53:1067-1071).
- Risk factors include having an inability to tan, fair skin that sunburns easily, and a history of intensive sun exposure at a young age.
- Annual dermatologic skin screening is recommended.

Rare Complications of mAb 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 mAb in such settings is not recommended. It is unclear if re-challenge with alternative anti-CD20 mAb poses the same risk of recurrence. An alternative anti-CD20 mAb could be used for patients with intolerance (including those experiencing severe hypersensitivity reactions requiring discontinuation of chosen anti-CD20 mAb).

Rituximab Rapid Infusion and Subcutaneous Administration

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

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Recurrent Sinopulmonary Infections (requiring IV antibiotics or hospitalization)

- Antimicrobials as appropriate
- Evaluate serum IgG, if <500 mg/dL
  - Begin monthly IVIG-0.3–0.5 g/kg or may substitute a subcutaneous immunoglobulin (SCIG) product given weekly at appropriately adjusted equivalent doses
  - Adjust dose/interval to maintain nadir level of approximately 500 mg/dL

Thromboprophylaxis

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

Tumor Flare Reactions

- Management of tumor flare is recommended for patients receiving lenalidomide
- Painful lymph node enlargement or lymph node enlargement with evidence of local inflammation, occurring with treatment initiation; may also be associated with spleen enlargement, low-grade fever, and/or rash
- Treatment:
  - Steroids (eg, prednisone 25–50 mg PO daily for 5–10 days)
  - Antihistamines for rash and pruritus (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)

Continued

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SUPPORTIVE CARE FOR PATIENTS WITH CLL/SLL

Vaccination

- **Avoid all live vaccines**
- **Annual influenza vaccine[b] (live attenuated influenza vaccine should be avoided)**
- **Pneumococcal vaccine**
  - **Pneumococcal polysaccharide vaccine (PPSV23) every 5 years or to maintain protective serologic antibody levels based on serologic testing.**
  - **The pneumococcal conjugate vaccine (PCV20) should be administered to newly diagnosed patients who are pneumococcal vaccine-naïve, followed by PPSV23 at least 8 weeks later. Subsequent doses of PPSV23 should follow current PPSV23 recommendations for adults at high risk. For patients who have previously received PPSV23, the PCV20 dose should be given at least 1 year after the last PPSV23 dose. For those who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after the PCV20 dose.**
  - **Pneumococcal antibody responses to some serotypes in PCV7 and PCV13 were decreased following co-administration of the meningococcal conjugate vaccine (MenACWY-D), PCV-7, and PCV13. Therefore, PCV7 and PCV13 should not be given with MenACWY-D but can be given with MenACWY-CRM.**
- **Zoster vaccine recombinant, adjuvanted for treatment-naïve patients or those treated with BTKi**
- **COVID-19 vaccination is recommended for all patients with CLL/SLL.**
  - **Early data suggest that the protective response rate to COVID-19 vaccination may be lower in individuals with CLL/SLL, regardless of CLL/SLL treatment status. Therefore, patients with CLL/SLL who have been vaccinated should maintain precautions recommended for unvaccinated individuals, such as mask wearing, social distancing, and diligent hand hygiene, until additional data are available to further clarify their risk.**
  - **The correlation, if any, between antibody titers against spike protein and protective immunity in this population has not been established, and the duration of any protection is unknown. Therefore, no recommendations can be made regarding antibody testing or actions based on antibody test results. Furthermore, tests are not available to assess cellular immunity post–COVID-19 vaccination. Additional updated general information is available from NCCN: Cancer and COVID-19 Vaccination.**
  - **Consider COVID prophylaxis with tixagevimab and cilgavimab for all patients with CLL/SLL.**

[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]		
Preferred regimens	**Other recommended regimens**	**Useful in certain circumstances**
• Acalabrutinib[f] ± obinutuzumab (category 1) • Venetoclax[f,g] + obinutuzumab (category 1) • Zanubrutinib[f] (category 1)	• Ibrutinib (category 1)[f,h] • Bendamustine[l] + anti-CD20 mAb[d,j,k] • Chlorambucil + obinutuzumab[l] • Obinutuzumab[l] • High-dose methylprednisolone (HDMP) + rituximab or obinutuzumab (category 2B; category 3 for patients <65 y without significant comorbidities) • Ibrutinib[f] + obinutuzumab[l] (category 2B) • Ibrutinib[f] + rituximab[p] (category 2B) • Ibrutinib + venetoclax[f,g] (category 2B)	(consider for IGHV-mutated CLL in patients age <65 y without significant comorbidities) • FCR (fludarabine, cyclophosphamide, rituximab)[m,n,o]

See Footnotes on CSLL-D 4 of 6

See Suggested Regimens for Second-line and Third-line Therapy for CLL/SLL without del(17p)/*TP53* mutation (CSLLL-D 2 of 6)

See Therapy for Relapsed or Refractory Disease After Prior BTKi- and Venetoclax-Based Regimens for CLL/SLL without del(17p)/*TP53* mutation (CSLL-D 2 of 6)

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

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

SECOND-LINE THERAPY OR THIRD-LINE THERAPY		
Preferred regimens • BTKi ▸ Acalabrutinib[f,q] (category 1) ▸ Zanubrutinib[f,q] • BCL-2 inhibitor ▸ Venetoclax[f,g] + rituximab[e] (category 1)	**Other recommended regimen** • Ibrutinib (category 1)[f,h] • Venetoclax[f,g]	**Useful in certain circumstances** (for relapse after a period of remission if previously used as first line therapy) • Retreatment with venetoclax[f,g] + obinutuzumab

THERAPY FOR RELAPSED OR REFRACTORY DISEASE AFTER PRIOR BTKi-AND VENETOCLAX-BASED REGIMENS[e]
Other recommended regimens • PI3K inhibitors[f] (alphabetical order) ▸ Duvelisib ▸ Idelalisib ± rituximab • CIT or Immunotherapy ▸ Bendamustine + rituximab[k] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities) ▸ FCR[n,o,p] ▸ Lenalidomide ± rituximab ▸ Obinutuzumab ▸ HDMP + rituximab or obinutuzumab (category 2B)

See Footnotes on CSLL-D 4 of 6

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

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

FIRST-LINE THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f] ± obinutuzumab • Venetoclax[f,g] + obinutuzumab • Zanubrutinib[f]	• Alemtuzumab[r] ± rituximab • HDMP + rituximab • Ibrutinib[f,h] • Obinutuzumab • Ibrutinib + venetoclax[f,g] (category 2B)

SECOND-LINE AND SUBSEQUENT THERAPY[e]	
Preferred regimens	**Other recommended regimens**
• Acalabrutinib[f,q] (category 1) • Venetoclax[f,g] + rituximab (category 1) • Venetoclax[f,g] • Zanubrutinib[f,q]	• Ibrutinib[f,h] (category 1) Alemtuzumab[r] ± rituximab • Duvelisib[f] • HDMP + rituximab • Idelalisib[f] ± rituximab[s] • Lenalidomide[t] ± rituximab

See Footnotes on CSLL-D 4 of 6

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

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

[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 mAb is not recommended in patients experiencing rare complications (eg, mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis). It is unclear whether re-challenge with alternative anti-CD20 mAbs poses the same risk of recurrence.
[e] An U.S. Food and Drug Administration (FDA)-approved biosimilar is an appropriate substitute for rituximab.
[f] See Special Considerations for the Use of Small-Molecule Inhibitors (CSLL-F).
[g] See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[h] The panel consensus to list ibrutinib under "other recommended regimens" is based on the toxicity profile. A baseline assessment of cardiac function should be done prior to initiation of ibrutinib. In patients with no intolerance, ibrutinib can be continued until disease progression.
[i] For patients age ≥65 y or patients age <65 y with significant comorbidities (creatinine clearance <70 mL/min) dose is 70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated.
[j] Anti-CD20 mAbs include: rituximab or obinutuzumab.
[k] Not recommended for frail patients.
[l] Recommended only for patients age ≥65 y or patients age <65 y with significant comorbidities (creatinine clearance [CrCl] <70 mL/min).
[m] Data from the CLL10 study confirmed the superiority of FCR over bendamustine + rituximab (BR) in younger patients. For patients >65 y, the outcome was similar for both regimens with less myelosuppression and infection for BR. FCR was associated with improved PFS (with a plateau in PFS beyond 10-year follow-up) in patients with mutated IGHV without del (17p)/*TP53* mutation (Thompson P, et al. Blood 2016;127:303-309).
[n] See Discussion for further information on oral fludarabine.
[o] 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.
[p] Recommended only for patients age <65 y without significant comorbidities.
[q] Acalabrutinib or zanubrutinib has not been shown to be effective for ibrutinib-refractory CLL with BTK C481S mutations. Patients with ibrutinib intolerance have been successfully treated with acalabrutinib or zanubrutinib without recurrence of symptoms.
[r] While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Alemtuzumab is less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation. See Treatment and Viral Reactivation (CSLL-C 1 of 4).
[s] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or NCI CTCAE grade ≥3 neutropenia or grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).
[t] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Andritsos L, et al. J Clin Oncol 2008;26:2519-2525; Wendtner C, et al. Leuk Lymphoma 2016;57:1291-1299.

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SUGGESTED TREATMENT REGIMENS
REFERENCES

Acalabrutinib ± obinutuzumab
Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia. Leukemia 2022;36:1171-1175.
Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus Ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. J Clin Oncol 2021; 39:3441-3452.
Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2020;38:2849-2861.
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.
Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica 2021;106:2364-2373.

Alemtuzumab ± rituximab
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.
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.

Bendamustine + rituximab or obinutuzumab
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.
Sharman JP, Burke JM, Yimer HA, et al. Phase 2, multicenter GIBB study of obinutuzumab plus bendamustine in previously untreated patients with chronic lymphocytic leukemia. Leuk Lymphoma 2021;62:791-800.
Stilgenbauer S, Bosch F, Ilhan O, et al. Safety and efficacy of obinutuzumab alone or with chemotherapy in previously untreated or relapsed/refractory chronic lymphocytic leukaemia patients: Final analysis of the Phase IIIb GREEN study. Br J Haematol 2021;193:325-338.

Chlorambucil + obinutuzumab
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.
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.
Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020;21:1188-1200.

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.
Davids MS, Kuss BJ, Hillmen P, et al. Efficacy and safety of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL or SLL in the DUO Crossover Extension Study. Clin Cancer Res 2020;26:2096-2103.

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.

HDMP (high-dose methylprednisolone) + rituximab or obinutuzumab
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.
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.
Castro JE, Amaya-Chanaga CI, Velez Lujan J, et al. Obinutuzumab (Gazyva) and High-Dose Methylprednisolone (HDMP) Combination for Patients with Chronic Lymphocytic Leukemia (CLL) - a Phase Ib/II Study [abstract]. Blood 2017;130:Abstract 1730.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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SUGGESTED TREATMENT REGIMENS
REFERENCES

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 2020;34:787-798.

Barr PM, Owen C, Robak T, et al. Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia [abstract]. J Clin Oncol 2021;39:Abstract 7523.

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;94:1353-1363.

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.

Woyach JA, Ruppert AS, Heerema NA, et al. Long-term results of Alliance A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab (BR) chemoimmunotherapy [abstract]. Blood 2021;138:Abstract 639.

Ibrutinib + obinutuzumab

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.

Ibrutinib + venetoclax

Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: Primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE Study. J Clin Oncol 2021;39:3853-3865. .

Ghia P, Allan JN, Siddiqi T, et al. First-line treatment with ibrutinib (Ibr) plus venetoclax (Ven) for chronic lymphocytic leukemia (CLL): 2-year post-randomization disease-free survival (DFS) results from the minimal residual disease (MRD) cohort of the phase 2 Captivate study [abstract]. Blood 2021;138:Abstract 68.

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 AK, Kahl BS, De Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018.

Lenalidomide ± rituximab

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.

Obinutuzumab

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.

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.

Venetoclax + obinutuzumab

Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020;21:1188-1200.

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, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-Year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. J Clin Oncol 2020;38:4042-4054.

Kater AP, Kipps TJ, Eichhorst B, et al. Five-year analysis of Murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx) [abstract]. Blood 2020;136:19-21.

Zanubrutinib

Tam C, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol 2022;23:1031-1043.

Hillmen P, Eichhorst B, Brown J, et al. First interim analysis of alpine study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. EHA 2021 LBA 1900.

Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. Haematologica 2020;106:2354-2363.

Shadman M, Sharman JP, Levy MY, et al. Phase 2 study of zanubrutinib in patients with relapsed/refractory B-cell malignancies intolerant to ibrutinib/acalabrutinib [abstract]. Blood 2020;136:51-52.

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

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

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

Footnotes on CSLL-E 2 of 2

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RESPONSE DEFINITION AFTER TREATMENT FOR CLL/SLL[a]

Minimal Residual Disease (MRD) Assessment:

- **Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of 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}.[j,k,l]**
- **MRD evaluation should be performed using an assay with a sensitivity of 10^{-4} according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method.**

[a] Hallek M, Cheson B, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.
[b] Isolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.
[c] Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).
[d] Spleen size is considered normal if <13 cm. There is no firmly established international consensus on the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.
[e] Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: Extended off-treatment follow-up from the randomized CLL14 study. J Clin Oncol 2021;39:4049-4060.
[f] Kater AP, Kipps TJ, Eichhorst B, et al. Five-year analysis of murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab (VenR) therapy (Tx) [abstract]. Blood 2020;136:19-21.
[g] 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.
[h] Rawstron AC, Kreuzer KA, Soosapilla A, et al. Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. Cytometry B Clin Cytom 2018;94:121-128.
[i] Wierda WG, Rawstron A, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. Leukemia 2021;35:3059-3072.
[j] 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.
[k] 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.
[l] 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

- **Most common adverse events (occurring in ≥20% of patients), adverse events of special interest, and drug interactions are summarized in the tables below.**
- **Please refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.**

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TABLE 1: SPECIAL CONSIDERATIONS FOR THE USE OF IRREVERSIBLE BTK INHIBITORS[a]

	Acalabrutinib	Ibrutinib	Zanubrutinib
FDA-approved use	CLL/SLL	CLL/SLL	Relapsed or refractory mantle cell lymphoma after 1 prior therapy
Dose	100 mg PO every 12 hours	420 mg PO once daily	160 mg PO twice daily or 320 mg PO once daily
Lymphocytosis	Upon initiation of treatment, transient increase in absolute lymphocyte count occurs in most patients, which does not signify disease progression. Can recur after re-initiation of therapy.	Upon initiation of treatment, transient increase in absolute lymphocyte count occurs in most patients, which does not signify disease progression. Can recur after re-initiation of therapy.	Upon initiation of treatment, transient increase in absolute lymphocyte count occurs in most patients, which does not signify disease progression. Can recur after re-initiation of therapy.
Most common adverse events (AEs) (all grades)	Neutropenia (23%); anemia (53%); thrombocytopenia (32%); headache (39%); fatigue (28%); musculoskeletal pain (32%); bruising (21%); rash (25%); nausea (22%)	Neutropenia (53%); thrombocytopenia (69%); anemia (43%); diarrhea (59%); nausea (20%); musculoskeletal pain (25%); fatigue (33%); bruising (51%); rash (25%)	Contusions (22%); neutropenia (17%); upper respiratory tract infection (18%); diarrhea (18%); nausea (16%); constipation (15%); rash (15%)
Adverse events of special interest (AESI)	Hypertension (8.6%, grade ≥3 [4.1%]); atrial fibrillation (9%, grade ≥3 [4.5%]); hemorrhage[b] (4%, grade ≥3 [3%]); pneumonia (17.7%, grade ≥3 [10.5%]); UTI (8.3%, grade ≥3 [1.1%])[c]	Hypertension (22.8%, grade ≥3 [8.7%]); atrial fibrillation (15.6%, grade ≥3 [3.4%]; hemorrhage[b] (8%, grade ≥3 [4%]); pneumonia (16.3%, grade ≥3 [8.7%]); UTI (13.5%, grade ≥3 [2.3%])[c]	Hypertension (6.4%, grade ≥3 [1.8%]); atrial fibrillation and flutter (2%, grade ≥3 [0.8%]); bleeding[b] (47%, grade ≥3 [4.6%]); pneumonia (8.3%, grade ≥3 [4%])[d]
Recommended antimicrobial prophylaxis	Consider PJP and varicella zoster virus (VZV) prophylaxis in patients at increased risk for opportunistic infections. Monitor for fungal infection.	Consider PJP and VZV prophylaxis in patients at increased risk for opportunistic infections. Monitor for fungal infection.	Consider PJP and VZV prophylaxis in patients at increased risk for opportunistic infections. Monitor for fungal infection.
Hepatic impairment	Avoid in patients with severe impairment.	Reduce dose for mild and moderate; avoid in patients with severe impairment.	Reduce dose in patients with severe impairment.
Drug interactions: CYP3A inhibitors	Avoid concomitant use of strong inhibitors. Reduce dose to 100 mg PO daily for concomitant use with moderate inhibitors.	Avoid strong inhibitors that are needed chronically. Reduce dose to 140 mg for concomitant use with moderate inhibitors.	Reduce dose to 80 mg once daily for concomitant use with strong inhibitors and 80 mg twice daily for moderate inhibitors.
Drug interactions: CYP3A inducers	Avoid concomitant use of strong inducers; if unavoidable, increase dose to 200 mg PO every 12 hours.	Avoid concomitant use of strong inducers.	Avoid concomitant use of moderate or strong inducers.
Drug interactions: Miscellaneous	Consider the benefit-risk in patients requiring anti-platelet or anticoagulant therapies. Avoid co-administration of capsule formulation with proton pump inhibitors and stagger dosing with H2-receptor antagonists and antacids; triazoles and fluoroquinolones increase drug levels.	Consider the benefit-risk in patients requiring anti-platelet or anticoagulant therapies; triazoles and fluoroquinolones increase drug levels.	Consider the benefit-risk in patients requiring anti-platelet or anticoagulant therapies.

[a] At time of disease progression, transition to next therapy as soon as possible. Treatment-free interval should be as short as possible. It is safe to overlap with venetoclax while on BTK inhibitor.
[b] Hold 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure.
[c] Byrd J, et al. Acalabrutinib versus Ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. J Clin Oncol 2021;39:3441-3452.
[d] Tam C, et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. Haematologica 2020;106:2354-2363.

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TABLE 2: SPECIAL CONSIDERATIONS FOR THE USE OF PI3K INHIBITORS

	Duvelisib (P13Kγ & δ)	Idelalisib (P13Kδ)
FDA-approved use	Relapsed or refractory CLL/SLL after at least 2 prior therapies	Relapsed CLL in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.
Dose	25 mg PO twice daily	150 mg PO twice daily
Lymphocytosis	Upon initiation of treatment, transient increase in absolute lymphocyte count occurs in most patients, which does not signify disease progression. Can recur after re-initiation of therapy.	Upon initiation of treatment, transient increase in absolute lymphocyte count occurs in most patients, which does not signify disease progression. Can recur after re-initiation of therapy.
Most common adverse events (AEs) (all grades)	Neutropenia (34%); thrombocytopenia (17%); anemia (20%); nausea (24%); diarrhea or colitis (50%); rash (31%); fatigue (29%); pyrexia (26%); cough (25%); musculoskeletal pain (20%)	Diarrhea (55%); fatigue (34%); nausea (34%); cough (45%); pneumonia (30%); pyrexia (38%); rash (25%)
Adverse events of special interest (AESI)	Severe infections (31%); diarrhea (50%, grade ≥3 [23%]); rash (31%, grade ≥3 [9%]); pneumonitis without an infectious cause (5%, grade ≥3 [1%]); pneumonia (21%, grade ≥3 [15%])	ALT increased (50%, grade ≥3 [19%]); AST increased (41%, grade ≥3 [12%]); diarrhea (47%, grade ≥3 [14%]); pneumonia (25%, grade ≥3 [16%]); intestinal perforation and severe cutaneous reactions
Recommended antimicrobial prophylaxis	Provide PJP prophylaxis during treatment and continue until CD4+ T-cell count >200 cell/μL. Acyclovir or equivalent is often used to prevent VZV reactivation. Vigilance in testing for CMV reactivation in symptomatic patients is recommended. (See CSLL-C)	Provide PJP prophylaxis during treatment, interrupt therapy in patients with suspected PJP infection, and permanently discontinue if confirmed. Acyclovir or equivalent is often used to prevent VZV reactivation. Vigilance in testing for CMV reactivation in symptomatic patients is recommended. (See CSLL-C)
Hepatoxicity - ALT/ AST elevation	Monitor weekly for grade 2; withhold for grade 3 and resume when <3 X ULN; discontinue for grade 4.	Regular monitoring is recommended. Withhold if >5 X ULN and continue to monitor AST, ALT, and total bilirubin weekly until resolved; resume at a reduced dose. Discontinue if ALT/AST >20 x ULN.
Drug interactions: CYP3A inhibitors	Monitor when coadministered with moderate or strong inhibitors. Reduce dose to 15 mg twice daily with strong inhibitors.	Avoid concomitant use of strong inhibitors; if concomitant use is unavoidable, close monitoring is required.
Drug interactions: CYP3A inducers	Avoid concomitant use of strong inducers.	Avoid concomitant use of strong inducers.
Drug interactions: CYP3A substrates	Monitor when coadministered with sensitive substrates.	Avoid concomitant use of sensitive substrates.
Drug interactions: Miscellaneous	Avoid concomitant use of other drugs that cause diarrhea.	Avoid concomitant use of other drugs that cause diarrhea.

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TABLE 3: SPECIAL CONSIDERATIONS FOR THE USE OF BCL-2 INHIBITOR

Venetoclax (BCL-2)	
FDA-approved use	CLL or SLL
Dose	5-week ramp-up to 400 mg PO daily[e]
Most common adverse events (AEs) (≥20%)	Cytopenias,[f] diarrhea, nausea, upper respiratory tract infection, cough, musculoskeletal pain, fatigue, edema
Adverse events of special interest (AESI)	TLS (risk based on renal function [CrCl <80 mL/min] and tumor burden); see CSLL-G for prophylaxis and monitoring; neutropenia with infection or fever (4%–6%); dose modifications may be required for grade 4 hematologic toxicities.
Recommended antimicrobial prophylaxis	Consider fluoroquinolone prophylaxis during neutropenia; consider fungal prophylaxis during neutropenia.
Drug interactions: CYP3A inhibitors	Concomitant use with strong inhibitors at initiation and during ramp-up phase is contraindicated. Alternative medications should be considered. Reduce dose by at least 50% during initiation, ramp-up, and maintenance phase for concomitant use with moderate CYP3A or P-glycoprotein inhibitors.
Drug interactions: CYP3A inducers	Avoid concomitant use of strong and moderate inducers. Concomitant use with a strong inducer may decrease efficacy.
Drug interactions: Miscellaneous	Increase INR monitoring if used with warfarin. Avoid concomitant use of P-glycoprotein substrates; if unavoidable, separate dosing by 6 hours

[e] Initiation and accelerated escalation (20–400 mg over 3 weeks) with close inpatient tumor lysis syndrome (TLS) monitoring (see CSLL-G) can be done in patients with high tumor burden and concern for rapid disease progression on or following BTK inhibitor therapy. For patients having a dosage interruption (>1 week during the ramp-up or >2 weeks after completion of ramp-up), reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary.

[f] 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.

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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/2022/208573s027lbl.pdf.
[b] Lymph node size should be evaluated by chest/abdominal/pelvic CT scan with contrast.
[c] Administer intravenous hydration for any patient who cannot tolerate oral hydration.
[d] Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
[e] Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[f] For patients at risk of TLS, monitor blood chemistries at 6–8 hours and at 24 hours at each subsequent ramp-up dose.

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DIAGNOSIS

ESSENTIAL:

- **A 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 standardized uptake value (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]**
  - **Classic Hodgkin lymphoma (CHL): Rare transformation to CHL demonstrates large Reed-Sternberg (RS) cells that express CD30, CD15, and PAX-5 but lack strong, uniform CD20 and CD45 (also lack co-expression of both OCT-2 and BOB.1). The background lymphocytes in those CHL cases are CD3+ T cells with a varying degree of admixed eosinophils, histiocytes, and plasma cells.[d]**

→ 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**

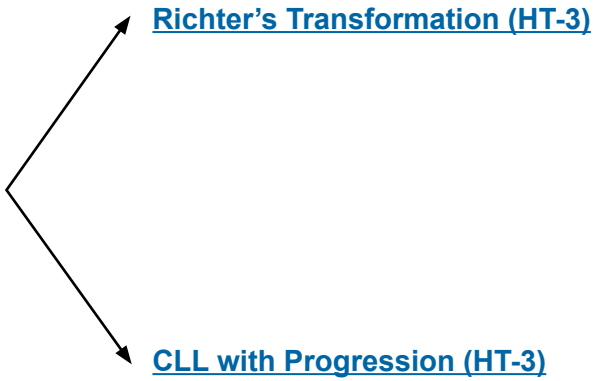
[a] While occasionally an increase in proliferative rate can be shown with Ki-67, this is not considered diagnostic of a transformation.
[b] Proliferation centers in CLL may express c-MYC and/or cyclin D1. This does not change the diagnosis.
[c] First, "CLL with expanded proliferation centers" or "accelerated 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" (CLL/PL) may occur when there are increased prolymphocytes in the blood (>10% to <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] Immunoglobulin gene rearrangement studies of CLL and histologically transformed tissue may be performed to establish the clonal relationship.

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

WORKUP

ESSENTIAL:
- History and physical exam with attention to node-bearing areas, including Waldeyer's ring, and the size of liver and spleen
- Performance status
- B symptoms
- CBC with differential
- Comprehensive metabolic panel
- LDH, uric acid
- Whole body PET/CT scan or chest/abdomen/pelvis CT with contrast of diagnostic quality
- Epstein-Barr virus (EBV) evaluation by EBV-latent membrane protein 1 (LMP1) or Epstein-Barr encoding region (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 childbearing age
- Discussion of fertility preservation[g]
- Human leukocyte antigen (HLA) typing



[f] 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 HBsAg and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

[g] Fertility preservation options include: sperm banking, semen cryopreservation, in IVF, or ovarian tissue or oocyte cryopreservation.

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NCCN Guidelines Version 1.2023
Histologic Transformation (Richter's) and Progression

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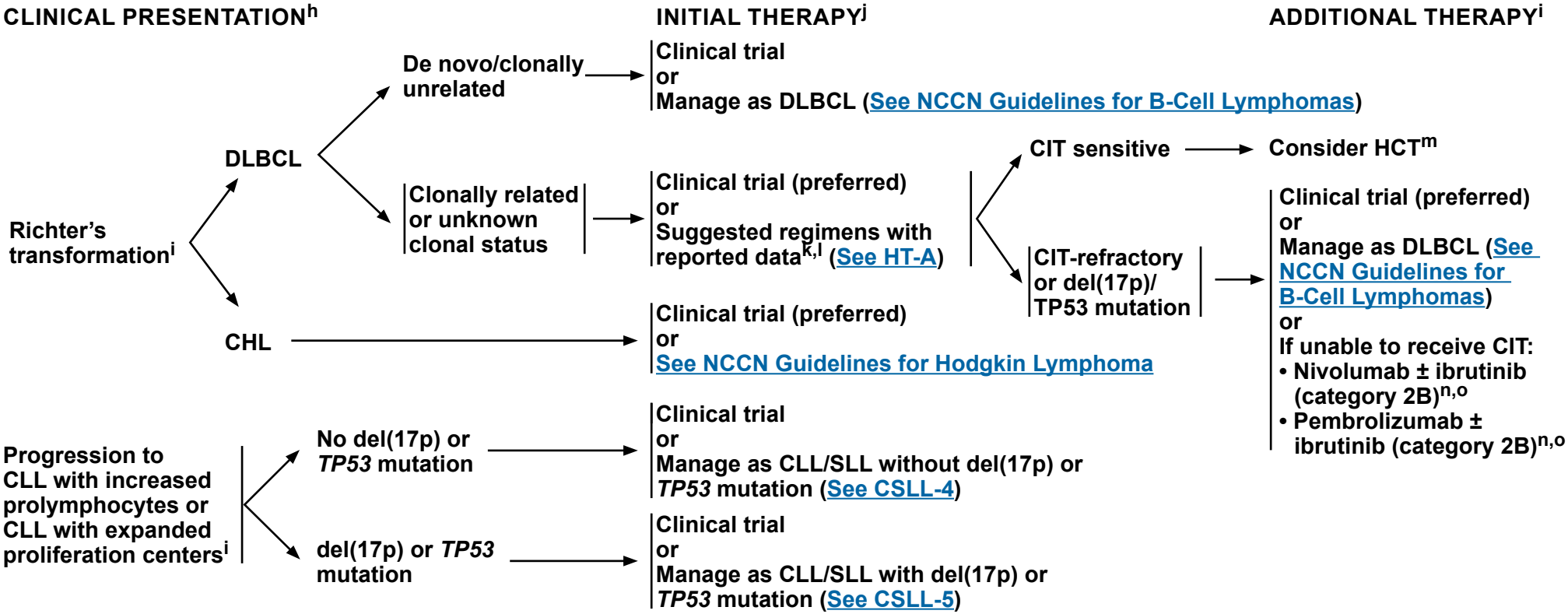

[h] "Accelerated CLL," "CLL with expanded proliferation centers," and CLL with increased prolymphocytes (CLL/PL) (defined on HT-1) are not considered Richter's transformation, but are associated with more aggressive disease and poorer outcome (Gine E, et al. Haematologica 2010;95:1526-1533; Ciccone M, et al. Leukemia 2012;26:499-508; Swerdlow S, et al. 2017 WHO Classification). Optimal management for these cases has not been established.

[i] For T-cell prolymphocytic leukemia (T-PLL), see NCCN Guidelines for T-Cell Lymphomas.

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

[k] 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 and optimal first-line therapy is not established. The regimens listed on HT-A are used at NCCN Member Institutions based on published data.

[l] 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.

[m] Cwynarski K, et al. J Clin Oncol 2012;30:2211-2217.

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

[o] 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 this patient population. Additional data will be forthcoming. See HT-A for references.

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SUGGESTED TREATMENT REGIMENS

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

- **Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab)**
- **HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine + rituximab**
- **OFAR (oxaliplatin, fludarabine, cytarabine, rituximab**
- **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)**

References (HT-A 2 of 2)

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SUGGESTED TREATMENT REGIMENS

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

Dose-adjusted-EPOCH-R

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

HyperCVAD + rituximab

Tsimberidou AM, Kantarjian HM, Cortes J, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. Cancer 2003;97:1711-1720.
Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. J Clin Oncol 2006;24:2343-2351.

OFAR.

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

RCHOP

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

Armand P, Murawski N, Molin D, et al. Pembrolizumab in relapsed or refractory Richter syndrome. Br J Haematol 2020;190:e117-e120.
Ding W, LaPlant BR, Call TG, et al. Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. Blood 2017;129:3419-3427.
Rogers KA, Huang Y, Dotson E, et al. Use of PD-1 (PDCD1) inhibitors for the treatment of Richter syndrome: experience at a single academic centre. Br J Haematol 2019;185:363-366.

Richter's Transformation to Hodgkin Lymphoma

Stephens D, Boucher K, Kander E, et al. Hodgkin lymphoma arising in patients with chronic lymphocytic leukemia: outcomes from a large multi-center collaboration Haematologica 2021;106:2845-2852.
Parikh SA, Habermann TM, Chaffee KG, et al. Hodgkin transformation of chronic lymphocytic leukemia: Incidence, outcomes, and comparison to de novo Hodgkin lymphoma. Am J Hematol 2015;90:334-338.

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ABBREVIATIONS

AEs	**adverse events**
AESI	**adverse events of special interest**
AIHA	**autoimmune hemolytic anemia**
ALC	**absolute lymphocyte count**
ALT	**alanine aminotransferase**
ANC	**absolute neutrophil count**
ASO-PCR	**allele-specific oligonucleotide polymerase chain reaction**
AST	**aspartate aminotransferase**
B-PLL	**B-cell prolymphocytic leukemia**
BTKi	**BTK inhibitor**
CBC	**complete blood count**
CHL	**classic Hodgkin lymphoma**
CIT	**chemoimmunotherapy**
CLL/SLL	**chronic lymphocytic leukemia/small lymphocytic lymphoma**
CMV	**cytomegalovirus**
CK	**complex karyotype**
CrCl	**creatinine clearance**
CT	**computed tomography**
DAA	**direct-acting antiviral**
DLBCL	**diffuse large B-cell lymphoma**
EBV	**Epstein-Barr virus**
FISH	**fluorescence in situ hybridization**
FNA	**fine-needle aspiration**
G6PD	**glucose-6-phosphate dehydrogenase**
GVHD	**graft-versus-host disease**
HBcAb	**hepatitis B core antibody**
HBsAg	**hepatitis B surface antigen**
HBV	**hepatitis B virus**
HCT	**hematopoietic cell transplant**
HCV	**hepatitis C virus**
HDMP	**high-dose methylprednisolone**
IGHV	**immunoglobulin heavy chain variable region gene**
IHC	**immunohistochemistry**
ITP	**immune thrombocytopenic purpura**
IVF	**in vitro fertilization**
IVIG	**intravenous immunoglobulin**
JC	**John Cunningham**
LDH	**lactate dehydrogenase**
mAb	**monoclonal antibody**
MBL	**monoclonal B-cell lymphocytosis**
MCL	**mantle cell lymphoma**
MenACWY (MenACWY-D and MenACWY-CRM)	**Meningococcal conjugate vaccine**
MRD	**minimal residual disease**
MUGA	**multigated acquisition**
NGS	**next-generation sequencing**
PCV (PCV7, PCV13 and PCV20)	**Pneumococcal conjugate vaccines**
PET	**positron emission tomography**
PFS	**progression-free survival**
PI3K	**phosphoinositide 3-kinase**
PJP	**pneumocystis jirovecii pneumonia**
PPSV23	**pneumococcal polysaccharide vaccine**
RS	**Reed-Sternberg**
RT	**radiation therapy**
qPCR	**quantitative RT-PCR**
RT-PCR	**reverse transcription polymerase chain reaction**
TLS	**tumor lysis syndrome**
ULN	**upper limit of normal**
UTI	**urinary tract infection**
VZV	**varicella zoster virus**

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.

Discussion

This discussion corresponds to the NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Last updated: June 3, 2022.

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 2022, an estimated 20,160 people will be diagnosed with CLL in the United States, and an estimated 4410 people will die from the disease.[1]

CLL and SLL are essentially 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 circulating in blood in addition to being resident in bone marrow and lymphoid tissue, while in SLL, the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues and there are few (if any) abnormal lymphocytes circulating in blood.

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 CLL and SLL published since the previous Guidelines update using the following search terms: chronic lymphocytic leukemia/small lymphocytic lymphoma, Richter syndrome, and histologic transformation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[3]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: 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 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 three 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*

IGHV 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]

IGHV mutation status is a predictor of high response rates and improved overall survival (OS) in patients treated with FCR (fludarabine, cyclophosphamide, and rituximab).[14-16] In the CLL8 trial (FCR vs. FC [fludarabine/cyclophosphamide] as first-line therapy), FCR was associated with significantly longer progression-free survival (PFS; median not reached compared to 42 months for FC; $P < .001$) and OS (5-year OS rate was 86% compared to 80% for FC) in the subgroup of patients with IGHV-mutated CLL.[14] The survival benefit was seen across all cytogenetic subgroups including del(11q), except for patients with del(17p) and normal karyotype. However, the IGHV mutation status did not have an impact on overall response rate (ORR) in this trial. In a phase II study of 300 patients with previously untreated CLL, minimal residual disease (MRD) negativity was achieved in 51% of patients with mutated IGHV, with a PFS rate of 80% at 13 years.[15] In a multivariable analysis, unmutated IGHV and del(17p) by conventional karyotyping were significantly associated with inferior PFS. Long-term PFS was notable, particularly for patients with mutated *IGHV*, with a plateau on the PFS curve beyond 10 years. In the CLL10 study that evaluated FCR versus bendamustine/rituximab (BR) as first-line therapy for CLL without del(17p), the PFS benefit of FCR was significant in physically fit patients less than 65 years and in patients with mutated *IGHV*.[16] Among patients with a mutated *IGHV,* the median PFS was not reached for FCR compared to 55 months for BR ($P = .089$).

Cytogenetic Abnormalities

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.[17]

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).[17] 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.[13,18] 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.[17] *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.[19-23]

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.[24] 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.[13,25,26]

In the CLL4 trial (chlorambucil vs. fludarabine vs. 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 of PFS and age was an independent predictor of OS. In the long-term follow-up from the CALGB 9712 study (concurrent vs. sequential fludarabine and rituximab as first-line therapy), del(17p) or del(11q) were independent predictors of shorter survival.[27]

Cell Surface Markers

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.[28-32] CD38 expression (≥30%) [7,11,13,33-35] and/or ZAP-70 (≥20%) are associated with shorter PFS and OS outcomes.[36-41] In addition, it was suggested that ZAP-70 positivity may be a stronger predictor of clinical outcomes than *IGHV* mutation status or CD38.[39-41] 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.[42-44]

Beta-2 Microglobulin

Beta-2 microglobulin is readily measured by standard laboratory evaluation of blood samples, and an elevated level of serum beta-2 microglobulin was shown to be a strong independent prognostic indicator for treatment-free interval, response to treatment, and OS in patients treated with first-line chemoimmunotherapy.[45,46] However, it is influenced in a CLL disease-independent manner by renal dysfunction.

Prognostic Models

Several prognostic models incorporating traditional and newer prognostic markers have been developed for the risk stratification.[47-52]

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 three different risk groups (low, intermediate, and high).[47] 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.[47] Several studies have independently confirmed the utility of this prognostic index in estimating both survival probability and time-to-first treatment (TTFT) in patients with untreated CLL, including those with early-stage (Rai stage 0) disease.[48,49]

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.[50] This model may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention.

The 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.[51] The 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.[52] The 5-year OS rates were significantly different between these risk groups (93%, 79%, 63%, and 23%, respectively). The 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.[53] The International Prognostic Score for Early-Stage CLL (IPS-E) has been proposed (based on the analysis of individual patient data in an international cohort of 4933 patients) to predict the likelihood of treatment requirement in patients with early-stage CLL.[54] The IPS-E score stratifies patients with early-stage CLL into three risk groups with significantly different TTFT. The cumulative risk for the need of treatment after 1 and 5 years of observation was 14% and 61%, respectively, for IPS-E high-risk patients compared to 2% and 28% for intermediate-risk patients and <0.1% and 8% for low-risk patients. These findings need to be validated in a prospective clinical trial.

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.[55-60] 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].[61] 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 BR; $P < .05$).

Collectively, data from the 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 newer prognostic markers were generated in an era of chemotherapy or chemoimmunotherapy. Newer small-molecule inhibitor-based therapy has significantly improved survival outcomes, including for 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.

More recently, two prognostic models have been developed to predict the outcome of patients treated with targeted therapy.[63,64] The first prognostic model stratified patients treated with ibrutinib into three risk groups (high [3–4 points]; intermediate [2 points]; and low [0 points]) based on *TP53* aberrations, prior treatment, beta-2 microglobulin (≥5 mg/L), and LDH greater than 250 U/L.[63] The 3-year PFS rates were 47%, 74%, and 87% for the high-, intermediate-, and low-risk groups, respectively ($P < .0001$). The corresponding 3-year OS rates were 63%, 83%, and 93%, respectively ($P < .0001$). This model remained significant in the stratification of patients with treatment-naïve and relapsed/refractory CLL. The second prognostic model allows for the identification of high-risk patients with previously treated CLL who do not achieve a good outcome with available targeted therapies (ibrutinib, idelalisib, and venetoclax).[64] This prognostic model stratifies patients into three risk groups (low [score 0–1]; intermediate [score 2–3]; and high risk [score 4]) using serum beta-2 microglobulin (≥5 mg/dL), elevated LDH, hemoglobin (<110 g/L for women or <120 g/L for men), and time from initiation of last therapy (<24 months).

Complex Karyotype

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.[65-68] 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.[65] 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 less than 65 years were all independently associated with a risk for CLL progression.[69] In patients 65 years and older without CK or del(17p), the estimated cumulative incidence of CLL progression at 4 years was 2% compared to 44% in patients less than 65 years with CK and del(17p). A more recent retrospective analysis of greater than 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.

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.[70]

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.[71]

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 blood resulting in a transient lymphocytosis in most patients, which does not signify disease progression. Prolonged lymphocytosis following ibrutinib treatment was reported to represent the persistence of a quiescent clone and slow or incomplete resolution of lymphocytosis does not appear to impact outcome as measured by PFS.[72]

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.[73] The revised iwCLL response criteria allow for a new response category, "partial response (PR) with lymphocytosis (PR-L)," 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.

Minimal Residual Disease

Assessment of measurable residual disease (MRD; often referred to as minimal residual disease) has emerged as a highly sensitive indicator of

disease burden in patients with CLL, supporting the integration of MRD assessment as part of response evaluation in the context of clinical trials. MRD detection can be performed using either blood or bone marrow. A commercial next-generation DNA sequencing (NGS)-based assay has been reported to be more sensitive allowing for the detection of MRD at the level of 10^{-6} and is the only assay currently available in the United States that is cleared by the FDA.[74-77] NGS-based assays require collection of a pretreatment sample. Multicolor (≥4) flow cytometry (MRD flow) and allele-specific oligonucleotide IGHV real-time quantitative polymerase chain reaction (ASO IGH RQ-PCR) are the two other methods used for the detection of MRD at the level of 10^{-4} to 10^{-5} with significantly more supporting data from clinical trials. MRD flow is the most widely used method owing to extensive availability and reliable detection at the level of $<10^{-4}$.[75,78] ASO IGH RQ-PCR detects MRD (at the level of $<10^{-5}$); however, it is less widely used since it is expensive and more labor intensive.[79] Consensus recommendations for the methodology for MRD determination, assay requirements and tissue selection (blood vs. bone marrow), and the use of MRD in clinical practice versus clinical trials were published.[80,81]

Several randomized clinical trials showed that undetectable MRD (uMRD; $<10^{-4}$ detectable leukemic cells in blood or bone marrow) at end of treatment (EOT) with chemoimmunotherapy[82,83] or venetoclax-based combination regimens with CD20 monoclonal antibody (mAb) [84-88] or ibrutinib [89-91] is an independent predictor of improved survival among patients with newly diagnosed as well as relapsed/refractory CLL. None of these trials studied use of MRD to direct treatment.

In the combined analysis of two randomized phase III studies conducted by the German CLL Study Group (GCLLSG) (CLL8 and CLL10), MRD status at the end of chemoimmunotherapy correlated with better survival in a multivariate analysis.[82] Among patients who achieved complete response (CR) and PR, PFS was longer for those with MRD-negative CR and MRD-negative PR (61 months and 54 months, respectively) than those with MRD-positive CR and MRD-positive PR (35 months and 21 months, respectively).[82] 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, uMRD at the end of first-line chemoimmunotherapy with FCR correlated with longer PFS.[83] The median PFS was not reached for patients with uMRD compared to 38 months for those with detectable MRD ($P < .001$). MRD level (≤1% vs. >1%) after three courses of FCR predicted greater likelihood of achieving uMRD by the EOT (64% vs. 9%; $P < .001$). PFS was significantly longer for patients with MRD ≤1% versus >1% after three courses of FCR (median 73 months vs. 41 months, $P < .001$), but similar for <0.01% versus 0.01%–1%.

In the CLL14 study, at 3-month follow-up after EOT, the rate of uMRD in blood was significantly higher with venetoclax + obinutuzumab compared to chlorambucil + obinutuzumab (74% vs. 34%; $P < .0001$; 40% of patients had uMRD levels of 10^{-6} in the venetoclax + obinutuzumab arm vs. 7% in the chlorambucil + obinutuzumab arm) and the uMRD status at EOT also correlated with improved survival outcomes in both treatment arms.[84] The 3-year OS rate for venetoclax + obinutuzumab was 92% for patients with uMRD (MRD levels $<10^{-4}$) and 73% for those with detectable MRD (MRD level $>10^{-2}$).

In the MURANO study, the rate of uMRD at the EOT with venetoclax + rituximab (VenR) was 62% compared to 13% after EOT with BR, and the rate of uMRD as best MRD response at any time during the study was also higher with VenR (83% vs. 23%).[85] The 5-year follow-up data from the MURANO study also showed that uMRD at the EOT with VenR was associated with improved OS.[86] The estimated 3-year survival rate was 95% for patients who had uMRD without disease progression at the EOT

compared to 85% for those with MRD at EOT. Unmutated IGHV, del(17p), and genomic complexity (≥3 copy number variations) were associated with higher rates of conversion to detectable MRD and subsequent progressive disease after attaining uMRD at EOT. Pre-existing mutated *TP53*, *NOTCH1*, *and BIRC3* were associated with lower rates of initial attainment of uMRD among patients treated with VenR.[86,87]

Results from the MRD cohort of the phase II randomized CAPTIVATE study showed that fixed-duration first-line treatment with ibrutinib + venetoclax (ibrutinib lead-in for 3 cycles followed by ibrutinib + venetoclax for 12 cycles; 164 patients) resulted in high rates of uMRD in both blood (75%) and bone marrow (68%).[89] High uMRD rates were observed in patients across all risk groups including del(17p)/*TP53* mutation and unmutated IGHV. Among 86 patients with confirmed uMRD randomized to receive placebo or ibrutinib, the estimated 36-month PFS rates were not significantly different for the two treatment arms (95% for those assigned to placebo and 100% for those assigned to ibrutinib).[90] Among the 63 patients without confirmed uMRD randomized to receive ibrutinib + venetoclax or ibrutinib, post-randomization uMRD rates were higher with ibrutinib + venetoclax (69% in blood; 66% in bone marrow) than with ibrutinib (48% in blood; 42% in bone marrow).[90] The estimated 36-month PFS rates were 97% for patients in both treatment arms.[90]

In the phase III randomized GLOW study (evaluating fixed-duration ibrutinib + venetoclax vs. chlorambucil + obinutuzumab as first-line treatment for CLL in elderly or unfit patients), the uMRD (10^{-4}) rate was significantly higher for ibrutinib + venetoclax both in bone marrow (52% vs. 17%; $P < .0001$) and blood (55% vs. 39%; $P = .0259$).[91] uMRD (10^{-4}) in the bone marrow for ibrutinib + venetoclax was also higher in patients with unmutated IGHV (58% vs. 44% for those with mutated IGHV). The 12-month PFS rate at the EOT was greater than 90% for patients in the ibrutinib + venetoclax arm (irrespective of MRD status). In contrast, detectable MRD in blood was associated with earlier relapse in patients treated with chlorambucil + obinutuzumab.

These findings confirm that uMRD status after EOT with venetoclax-based combination regimens is a predictive marker for PFS. MRD assessment may be useful in clinical practice to provide insight into anticipated PFS duration following fixed-duration treatment, but not to reliably recommend treatment duration or in treatment decisions for patients on targeted therapy at the present time.

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.[92]

Pharmacokinetic (drug exposure) and pharmacodynamic (response) studies in the appropriate patient population are essential to demonstrate the efficacy and safety of the biosimilar.[93] 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.[93]

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.[92] However, alternating between the biosimilar and reference product is not recommended, if the biosimilar is not designated as interchangeable.

The guidelines recommend the use of an FDA-approved biosimilar as an appropriate substitute for rituximab. 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 these are biosimilar to rituximab in terms of safety and efficacy. These 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 treatment.

Diagnosis

The diagnosis of CLL requires the presence of at least 5 x 10^9/L monoclonal B-lymphocytes in the peripheral blood and the clonality of B cells should be confirmed by flow cytometry.[70] 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.[70] 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 lymphoid enhancer binding factor-1 (LEF1) may be helpful in the differential diagnosis of CLL, especially to exclude other CD5+ B-cell lymphoproliferative disorders—specifically mantle cell lymphoma.[94-97]

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.[98,99]

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* mutation percentage cut-off levels ranging from 1% to 5% have been studied.[100] In a retrospective analysis of 203 patients treated with the FCR regimen, higher cut off levels were incrementally associated with favorable PFS and OS, suggesting that *IGHV* mutation percentage is a continuous variable in patients treated with the FCR regimen.[101] A cut-off level of 2% or less IGHV mutation is routinely used in clinical practice to differentiate patients with IGHV-mutated CLL from those with IGHV-unmutated CLL.[102,103] Patients with IGHV-mutated CLL by this definition can have long-term PFS following FCR (54% at 13 years).[15] *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.[7,29,36,37] However, discordant results between *IGHV* mutation status and CD38 or ZAP-70 positivity have been reported in about 20% to 28% of

cases.[13,39,104] Furthermore, standardization and reproducibility of these markers across laboratories remain a challenge. Evaluation of CD38, CD49d, and ZAP-70 is not recommended outside the context of clinical trials.

Monoclonal B-Cell Lymphocytosis

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 that does not meet the diagnostic criteria for CLL.[105,106] An absolute monoclonal B-lymphocyte count of <5 x 10^9/L that is stable over a 3-month period in the absence of palpable lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder (ie, anemia, thrombocytopenia, constitutional symptoms, organomegaly) is defined as MBL.[107]

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.[108,109] 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.[110] 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.[111]

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.[106] 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.[47] 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.[112,113]

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.[70] 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. In a randomized prospective phase III study of patients with early-stage high-risk CLL, although FCR resulted in high ORR (93%) and significantly prolonged EFS (median not reached vs. 19 months; $P < .001$) compared to watch and wait, there was no significant OS benefit (5-year OS rate was 83% with FCR compared to 80% for watch and wait).[114]

These results confirm that "watch and wait" remains an appropriate treatment option for selected patients with early-stage high-risk CLL.

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.[70] Absolute lymphocyte count alone is not an indication for treatment and symptoms related to leukostasis are exceedingly rare in CLL patients.[70]

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 chemoimmunotherapy-based clinical trials, including the studies conducted by the GCLLSG.[115] 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.[116]

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.[116,117] In the CLL14 study, CIRS score greater than 6 or an estimated CrCl less than 70 mL/min was used as the eligibility criteria for patients with significant comorbidities.[118]

In patients with indications for initiating treatment, patient age, functional status, comorbidities, and the presence or absence of del(17p) or *TP53* mutation help direct treatment planning. Patients are stratified into three groups based on their functional status and presence or absence of comorbidities: patients 65 years or older or younger patients with

significant comorbidities (CrCl <70 mL/min), and patients less than 65 years without significant comorbidities.

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

First-Line Therapy

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

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

Preferred Regimens

BTKi (acalabrutinib ± obinutuzumab, ibrutinib, zanubrutinib) and venetoclax + obinutuzumab are included as preferred treatment options, based on the results of the phase III randomized studies (ELEVATE-TN, RESONATE-2, E1912, SEQUOIA, and CLL14).[118-124]

The efficacy data (ORR, PFS, and OS) are summarized in Table 1.

Acalabrutinib ± Obinutuzumab

The phase III ELEVATE-TN trial demonstrated that acalabrutinib ± obinutuzumab results in superior PFS versus chlorambucil + obinutuzumab in patients with previously untreated CLL.[120] Acalabrutinib + obinutuzumab was associated with a PFS benefit in patients with IGHV-unmutated CLL as well as IGHV-mutated CLL compared to chlorambucil + obinutuzumab. There was a trend towards improved OS for acalabrutinib ± obinutuzumab, despite crossover for disease progression in the chlorambucil + obinutuzumab arm, though longer follow-up is needed to confirm any OS benefit. At 48-month follow-up, longer PFS (87% vs. 78%) was seen with acalabrutinib + obinutuzumab compared to acalabrutinib, although the study was not planned or powered to compare the PFS benefit between the two acalabrutinib arms.

Acalabrutinib was granted broad FDA approval for the treatment of patients with untreated and relapsed/refractory CLL based on the results of the ELEVATE-TN trial. Acalabrutinib ± obinutuzumab is included with a category 1 recommendation for all patients with CLL without del(17p) or *TP53* mutation.

Ibrutinib

In the RESONATE-2 study, after a median follow-up of 5 years, ibrutinib resulted in significantly higher ORR ($P < .0001$) and significantly longer PFS rate ($P < .0001$) compared to chlorambucil in patients 65 years or older without del(17p).[121] With 57% of patients switching to ibrutinib after disease progression on chlorambucil, the estimated 5-year OS rate was also higher with ibrutinib (without censoring for crossover from chlorambucil). Ibrutinib also improved PFS compared to chlorambucil in patients with high-risk CLL and the estimated 5-year PFS rates were 79% and 67%, respectively, for patients with del(11q) and unmutated *IGHV*. Extended long-term data confirmed the sustained PFS benefit of ibrutinib as first-line therapy for patients with CLL, including those with high-risk genomic features of unmutated IGHV (HR, 0.109) or del(11q) (HR, 0.033).[122]

The Alliance North American Intergroup Study (A041202) showed primary benefit for ibrutinib and ibrutinib + rituximab in patients with unmutated IGHV (61% of patients had unmutated IGHV) rather than mutated IGHV.[22,23] 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.

The panel consensus was to continue the listing of ibrutinib with a category 1 recommendation for patients 65 years or older or younger patients with significant comorbidities.

Ibrutinib monotherapy was approved for first-line therapy for all patients based on the results of the RESONATE-2 study that established the efficacy of ibrutinib monotherapy as first-line therapy only in patients 65 years or older without del(17p).[121,122] The ECOG-ACRIN cancer research group [E1912) study and the FLAIR study (median age: 62 years; patients >75 years and >20% del 17p cells were excluded) showed that ibrutinib + rituximab was more effective than FCR for patients 70 years or less without del(17p)/*TP53* mutation, especially for those with unmutated *IGHV,* indicating that ibrutinib may also be an appropriate option for younger patients with *IGHV* unmutated CLL.[125,126]

Therefore, ibrutinib is also included as a category 1 recommendation for patients less than 65 years without del(17p) or *TP53* mutation.

Venetoclax + Obinutuzumab

The CLL14 study established venetoclax + obinutuzumab as an effective fixed-duration chemotherapy-free first-line treatment option with significantly improved PFS compared to chlorambucil + obinutuzumab in patients 65 years or older, or younger patients with comorbidities (CIRS score >6 or an estimated CrCl <70 mL/min).[118] The uMRD rate at the EOT was significantly higher with venetoclax + obinutuzumab (74% vs. 34%; *P* < .0001), and this combination was also associated with lower rate of conversion to MRD-positive status 1 year after treatment.[84,118]

The efficacy of venetoclax + obinutuzumab in patients less than 65 years of age without significant comorbidities was not established in a randomized clinical trial, although preliminary data from a more recent randomized phase III study (CLL13) suggest that first-line therapy with venetoclax + obinutuzumab may be more effective than chemoimmunotherapy (FCR or BR) in patients less than 65 years of age in terms of uMRD rate in blood (87% vs. 52% for chemoimmunotherapy with FCR or BR; *P* <.0001) and bone marrow (73% vs. 37% for chemoimmunotherapy with FCR or BR) at 15 months.[88]

Venetoclax + obinutuzumab was granted broad FDA approval for the treatment of patients with CLL and is included with a category 1 recommendation for patients 65 years or older or younger patients with significant comorbidities.[118,124] The panel members agreed that venetoclax + obinutuzumab is also an appropriate fixed-duration chemotherapy-free treatment option for younger patients without comorbidities and the panel consensus was to include venetoclax + obinutuzumab with a category 2A recommendation for patients less than 65 years of age without significant comorbidities.

Zanubrutinib

Zanubrutinib is a highly selective/specific irreversible BTK inhibitor that is FDA-approved for the treatment of Waldenström's macroglobulinemia and relapsed/refractory mantle cell lymphoma. In the phase III SEQUOIA study, zanubrutinib resulted in higher ORR (95% vs. 85%) and statistically significant improvement in PFS compared to bendamustine and rituximab (BR) in patients with untreated CLL without del (17p)/*TP53* mutation (HR 0.42; *P* <.0001).[123] PFS benefit was also observed in patients with del(11q) and unmutated IGHV (HR, 0.24; *P* < .0001) but not for patients with mutated IGHV (HR, 0.67; *P* = .0929), which may be due to the relatively short follow-up.

Based on the results of the SEQUOIA study, zanubrutinib is included with a category 2A recommendation.

Other Recommended Regimens

Bendamustine + Anti-CD20 Monoclonal Antibody

In the CLL10 study, there was no significant difference in PFS between BR and FCR as first-line therapy for CLL without del(17p) in patients greater than 65 years, although the PFS benefit of FCR was significant in physically fit patients less than 65 years.[127] The incidence of severe neutropenia and infections was significantly more frequent in the FCR arm, especially among patients greater than 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).[127] After a median follow-up of 58 months, the incidences of secondary AML and MDS were significantly higher in the FCR arm (7% for patients >65 years and 3% in patients <65 years) compared to BR (1% for both older and younger patients).

Bendamustine + anti-CD20 mAb (rituximab or obinutuzumab) may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is included as an option for patients 65 years or older or younger patients with significant comorbidities and for patients less than 65 years without significant comorbidities.[127-130]

Chlorambucil + Obinutuzumab

The 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.[131] The subsequent phase III iLLUMINATE study demonstrated ibrutinib + obinutuzumab as a more effective first-line therapy than chlorambucil + obinutuzumab for patients 65 years or older and younger patients with comorbidities (median age was 71 years; ibrutinib + obinutuzumab, n = 113; chlorambucil + obinutuzumab, n = 116).[132]

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 patients 65 years or older 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*.[14,15,125,127]

The E1912 study showed that ibrutinib + rituximab was more effective than FCR for patients 70 years or less without del(17p)/*TP53* mutation.[125] 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 less than 65 years without significant comorbidities.

The panel emphasizes that FCR is the preferred first-line therapy option for IGHV-mutated CLL in patients less than 65 years without significant comorbidities since the FCR regimen results in high response rates and improved OS in this specific subgroup of patients with previously untreated CLL.[14,15,127]

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.[133-135] 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 + rituximab (FR) is included as an option for patients less than 65 years without significant comorbidities.[27] FR is not recommended for CLL with del(11q), since outcomes for CLL with del(11q) are better with chemoimmunotherapy containing an alkylating agent.

HDMP + Rituximab

High-dose methylprednisolone (HDMP) + rituximab is included with a category 2B recommendation for all patients, regardless of patient's age and comorbidities.[136] 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 E1912 study and the FLAIR study showed that ibrutinib + rituximab was more effective than FCR for patients 70 years or less without del(17p)/*TP53* mutation, especially for those with unmutated *IGHV,* indicating that ibrutinib may also be an appropriate option for younger patients with *IGHV* unmutated CLL.[125,126]

The results of other randomized phase III trials showed that ibrutinib + rituximab or obinutuzumab is more effective than chemoimmunotherapy for previously untreated CLL without del(17p) or *TP53* mutation in patients 65 years or older or younger patients with comorbidities.[22,23,132,137] Ibrutinib + obinutuzumab was approved by the FDA for first-line therapy based on the results of the iLLUMINATE study.[132] However, the addition of rituximab to ibrutinib did not result in improvement in clinical outcomes compared to ibrutinib monotherapy [22,23,137] and there are no randomized clinical trials that compare ibrutinib vs. ibrutinib + obinutuzumab.

The majority of the panel members acknowledged that the results of two randomized studies did not show a benefit for the addition of rituximab to ibrutinib, and there are no randomized clinical trials that have compared ibrutinib versus ibrutinib + obinutuzumab.[22,23,137] In the Alliance North American Intergroup Study (A041202), the estimated 48-month PFS rates were 76% for both ibrutinib + rituximab and ibrutinib monotherapy.[23] 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.[137]

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 six cycles. Therefore, the consensus was that the longer PFS was more the result of continuous and indefinite treatment with ibrutinib, rather than due to the contribution of an anti-CD20 mAb (rituximab or obinutuzumab) during the first 6 months of treatment. Improved outcomes with addition of an anti-CD20 mAb may more likely be seen with fixed-duration treatment with this regimen.

Ibrutinib + obinutuzumab (for patients 65 years or older and younger patients with significant comorbidities) and ibrutinib + rituximab (for patients less than 65 years without significant comorbidities) are included with a category 2B recommendation.

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 panel members acknowledged that monotherapy with any of these agents is not an effective first-line treatment even for patients with comorbidities. 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 patients 65 years or older with significant comorbidities or decreased performance status for whom more intensive regimens are not appropriate.[130,138-140]

Obinutuzumab monotherapy is included with a category 2A recommendation and monotherapy with rituximab or chlorambucil is included with a category 3 recommendation for patients 65 years or older or younger patients with significant comorbidities.

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

There are limited data from prospective clinical studies on the efficacy of BTKis or BCL2 inhibitors as first-line therapy for patients with del(17p)/*TP53* mutated CLL.

Patients with del(17p) CLL were not eligible for enrollment in the RESONATE-2 study and the E1912 study.[121,125] In the RESONATE-2 study, 12 patients treated with ibrutinib had *TP53* mutation and after 6-year follow-up, the estimated 5-year PFS rate was 56% for this group of patients.[121] However, comparison between ibrutinib and chlorambucil could not be made since only three patients in the chlorambucil group had *TP53* mutation. In a phase II trial that included 35 treatment-naïve patients with del(17p)/*TP53* mutation (median age 62 years), ibrutinib resulted in an ORR of 96% (29% CR and 67% PR) and the estimated 5-year PFS and OS were 74% and 85%, respectively.[141]

In the ELEVATE-TN study, the PFS benefit for acalabrutinib ± obinutuzumab was seen across all patient subgroups including those with del(17p) or *TP53* mutation but only 14% of patients had del(17p) CLL.[120] The 48-month PFS rates were 75% and 76%, respectively, for acalabrutinib + obinutuzumab and acalabrutinib monotherapy in patients with del(17p) and/or *TP53* mutation.

In the CLL14 study, the PFS benefit for venetoclax + obinutuzumab was also seen across all patient subgroups including those with del(17p) or *TP53* mutation [del(17p) or mutated *TP53* were seen in only 8% and 12% of patients, respectively].[118]

In the phase III SEQUOIA study, patients with del(17p) were not part of the randomized cohort but were enrolled only to single-agent zanubrutinib or subsequently, to the combination of zanubrutinib and venetoclax. In the prospectively enrolled non-randomized cohort [109 patients with del(17p)/*TP53* mutated CLL], single-agent zanubrutinib resulted in an ORR of 95% (3% CR; 87% PR).[142] After a median follow-up of 18 months, the median PFS and OS were not reached. The estimated 18-month PFS rate and OS rates were 89% and 95%, respectively. The best ORR and 18-month PFS rates were 98% and 89%, respectively, for patients with high del(17p) (≥20%); 92% and 88%, respectively, for patients with low del(17p) (>7% to <20%).

Preferred Regimens

Enrollment in an appropriate clinical trial is recommended for patients with untreated del(17p) CLL.

Given currently available data, acalabrutinib ± obinutuzumab, ibrutinib, zanubrutinib, and venetoclax + obinutuzumab are included as preferred

treatment options for first-line therapy with a category 2A recommendation.[118,120,141,142]

Other Recommended Regimens

The panel emphasizes that the efficacy of BTKi (ibrutinib or acalabrutinib or zanubrutinib) 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 other recommended regimens (when BTKi or venetoclax is not deemed appropriate):

- Alemtuzumab ± rituximab[143-146]
- HDMP + rituximab[136]
- Obinutuzumab[138]

Second-Line and Subsequent Therapy

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

Acalabrutinib, ibrutinib, and venetoclax ± rituximab are also approved for the treatment of relapsed/refractory CLL/SLL based on the results of phase III randomized studies (ASCEND, RESONATE, and MURANO trials, respectively).[85,86,147-150] The PFS benefit compared to chemoimmunotherapy was seen across all patient subgroups including those with del(17p) or *TP53* mutation.

The efficacy data (ORR, PFS, and OS) from randomized clinical trials that have evaluated small-molecule inhibitors for relapsed/refractory CLL/SLL are summarized in Table 2.

BTK Inhibitors

In the ASCEND study, at a median follow-up of 36 months, the median PFS was not reached and the 36-month PFS rate was 66% for patients with del(17p)/*TP53* mutation assigned to acalabrutinib.[148] The phase III ELEVATE-RR trial demonstrated that acalabrutinib is non-inferior to ibrutinib in terms of PFS and was also associated with a more favorable safety profile in patients with relapsed/refractory del(17p) CLL.[151]

The final analysis of the RESONATE study showed that the presence of del(17p)/*TP53* mutation or CK was not associated with inferior PFS outcomes to ibrutinib.[149] 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. The phase II RESONATE-17 study established the efficacy and safety of ibrutinib in patients with relapsed or refractory del(17p) CLL (n =145), demonstrating an ORR of 83% (as assessed by the independent review committee [IRC]).[152]

Zanubrutinib also demonstrated activity in patients with relapsed/refractory CLL.[153-155] The first interim analysis of the randomized phase III study (ALPINE) showed that zanubrutinib was more effective than ibrutinib, resulting in significantly higher ORR and longer PFS in patients with relapsed/refractory CLL/SLL.[155] The ORR was also higher for zanubrutinib (83% vs. 54% for ibrutinib) in patients with del(17p)/*TP53* mutation.

BCL-2 Inhibitors

In the phase III randomized MURANO study that compared VenR versus BR in patients with relapsed/refractory CLL, VenR was superior to BR with longer PFS across all subgroups of patients, including those with del(17p) or *TP53* mutation (HR, 0.21 for del(17p); HR, 0.25 for *TP53* mutation), and uMRD at the EOT was higher for VenR (62% vs. 13% for BR).[85]

Venetoclax monotherapy also demonstrated efficacy in patients with relapsed or refractory del(17p) CLL, resulting in ORR of 77% (63% in patients who received prior therapy with BCRi (ibrutinib or idelalisib).[156] The estimated 24-month PFS and OS rates were 54% and 73%, respectively for the overall study population (50% and 55%, respectively, for patients who had received prior BCRi).

PI3K Inhibitors

Idelalisib + rituximab (IdR) and duvelisib also have demonstrated efficacy (in terms of median PFS) in randomized phase III studies for patients with relapsed/refractory CLL/SLL.[157-160]

IdR significantly prolonged survival in patients with del(17p) or *TP53* mutations compared with those treated with rituximab + placebo.[157] The median OS was 29 months for patients treated with IdR compared to 15 months for those treated with rituximab + placebo. Idelalisib monotherapy also has demonstrated activity in relapsed/refractory SLL.[161,162] The indication for idelalisib monotherapy in relapsed/refractory SLL was withdrawn by the manufacturer as they are unable to complete the required confirmatory studies following the FDA accelerated approval. While the panel acknowledged the change in the regulatory status of idelalisib, the panel consensus was to continue listing idelalisib monotherapy as an option for relapsed/refractory SLL, given demonstrated efficacy.[161,162]

Duvelisib also significantly extended median PFS (17 months vs. 9 months) compared to ofatumumab in the subgroup of patients with del(17p).[158] In the DUO crossover extension study (that evaluated the efficacy and safety of duvelisib monotherapy in patients with disease progression while receiving ofatumumab in the DUO trial), the ORR was 77% (61% PR) for the subset of 26 patients with del(17p) and/or *TP53* mutations.[159]

PI3K inhibitors are associated with increased risk of hepatotoxicity (transaminase elevations), severe diarrhea or colitis, pneumonitis, opportunistic infections, and febrile neutropenia.

Other Systemic Therapy Regimens

Chemoimmunotherapy regimens including FCR, BR ± ibrutinib, and FC + ofatumumab also demonstrated activity in patients with relapsed/refractory disease.[163-167]

HDMP + rituximab was effective in patients with heavily pretreated CLL (including fludarabine refractory disease), although it was associated with infectious complications (including opportunistic fungal infections) in about 30% of patients, which may necessitate adequate antiinfective prophylaxis and close monitoring for early signs of infections.[168,169]

Lenalidomide ± rituximab also has demonstrated activity in patients with relapsed/refractory disease.[170-172] However, the ORR was lower for lenalidomide + rituximab in the subgroup of patients with fludarabine-refractory CLL compared with those with fludarabine-sensitive CLL. Lenalidomide can be given as continuous or intermittent dosing for patients with CLL.[170] Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment.

Alemtuzumab + rituximab results in a higher ORR than that observed with alemtuzumab monotherapy and there was no significant difference in response rates between patients with fludarabine-sensitive and fludarabine-refractory disease.[173] 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.[174,175]

Obinutuzumab and ofatumumab (as monotherapy) also have demonstrated activity in patients with relapsed/refractory CLL/SLL. [130,176]

Ofatumumab monotherapy has demonstrated activity in patients with fludarabine-refractory CLL with bulky lymphadenopathy (>5 cm; BF-ref CLL) and was also effective and well tolerated in patients with FA-ref CLL and previous rituximab exposure.[176]

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

Preferred Regimens

- Acalabrutinib, ibrutinib, and VenR are included with a category 1 recommendation.[87,147-149]
- Zanubrutinib is included with a category 2A recommendation.[155]

Other Recommended Regimens

The following regimens are included as options for patients less than 65 years without significant comorbidities.

- FCR[163,164]
- Alemtuzumab ± rituximab (category 3)[173-175,177]
- BR + ibrutinib (category 3)[166]
- FC + ofatumumab (category 3)[167]

The following regimens are included as options for relapsed/refractory disease regardless of patient's age or comorbidities:

- BR (category 2B for patients 65 years or older or patients less than 65 years with significant comorbidities)[165]
- Idelalisib ± rituximab[157,161,162]
- Duvelisib[158-160]
- Lenalidomide ± rituximab[170-172]
- Obinutuzumab or ofatumumab[130,176]
- Venetoclax[178-181]
- HDMP + rituximab or obinutuzumab (category 2B)[168,169]

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

Preferred Regimens

- Acalabrutinib, ibrutinib, and VenR are included with a category 1 recommendation.[87,147-149]
- Zanubrutinib is included with a category 2A recommendation.[155]
- Venetoclax monotherapy is included with a category 2A recommendation.[156]

Other Recommended Regimens

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

- Alemtuzumab ± rituximab[173,177]
- Duvelisib[158-160]
- HDMP + rituximab[182]
- Idelalisib ± rituximab[157,161,162]
- Lenalidomide ± rituximab[170,171]
- Ofatumumab[183]

Special Considerations for the Use of Small-Molecule Inhibitors

Management of Adverse Events

BTK Inhibitors

Diarrhea, fatigue, arthralgia, infections, cytopenias, bleeding, and cardiovascular toxicities (including atrial fibrillation, ventricular arrhythmias, and hypertension) are the adverse events (AEs) associated with BTKis (Table 3).

Acalabrutinib and zanubrutinib have a more favorable toxicity profile due to the more selective/specific inhibition of BTK. In the ELEVATE-RR head-to-head trial of acalabrutinib vs. ibrutinib, treatment discontinuation due to AEs was lower with acalabrutinib (15% vs. 21% for ibrutinib).[151] Atrial fibrillation (9% vs.16%), hypertension (9% vs. 23%), and bleeding (38% vs. 51%) were less frequent with acalabrutinib compared to ibrutinib. Acalabrutinib was associated with a higher rate of headache (35% vs. 20% for ibrutinib), with only 2% of patients experiencing grade ≥3 headache. Zanubrutinib was also associated with a substantially lower rate of atrial fibrillation (2.5% vs. 10%) compared to ibrutinib in the ALPINE trial.[155] In contrast, neutropenia was more frequent with zanubrutinib (28% vs. 22% for ibrutinib); however, this did not translate into a higher rate of infection (60% with zanubrutinib vs. 63% for ibrutinib).

The benefit and risk of BTKis should be evaluated in patients requiring anti-platelet or anticoagulant therapies. Patients requiring warfarin were excluded from clinical trials evaluating acalabrutinib and ibrutinib, while the use of anticoagulants including warfarin was not restricted in clinical trials evaluating zanubrutinib. Concomitant administration of ibrutinib or acalabrutinib with warfarin should be avoided. Coadministration of acalabrutinib with proton pump inhibitors (PPIs) should be avoided. Zanubrutinib can be co-administered with anticoagulants including warfarin and gastric acid-reducing agents (PPIs, H2-receptor antagonists).

Hypertension should be managed with anti-hypertensives as appropriate. Headache is commonly observed with acalabrutinib early in the treatment course and can generally be managed with analgesics (eg, acetaminophen) and caffeine supplements. Monitoring for signs of bleeding, atrial fibrillation, and hypertension along with appropriate management is recommended for patients receiving BTKis.

Switching to alternate therapy can be considered, especially in patients with atrial fibrillation or hypertension that is not medically controllable.

Acalabrutinib and zanubrutinib were shown to be effective for the management of patients with ibrutinib intolerance.[184-186]

Hepatitis B virus (HBV) reactivation and invasive fungal infections have been rarely reported in patients treated with ibrutinib.[187,188] There currently are no sufficient data to recommended routine screening and prophylaxis.

PI3K Inhibitors

Hepatotoxicity (transaminase elevations), severe diarrhea or colitis, pneumonitis, opportunistic infections, and febrile neutropenia 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.[189] Close monitoring of transaminase levels is essential and concurrent administration of idelalisib or duvelisib with other hepatotoxic drugs should be avoided.

The addition of anti-CD20 mAb or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia.[190] Anti-infective prophylaxis for herpes simplex virus (HSV), Pneumocystis jirovecii pneumonia (PJP), and cytomegalovirus (CMV) reactivation are recommended for patients receiving idelalisib or duvelisib.

BCL-2 Inhibitors

TLS was an important side effect of venetoclax in early clinical trials. Initiation at lower dose (20 mg for one week) and gradual step-wise ramp-up over 5 weeks to target dose (400 mg daily) along with TLS prophylaxis is recommended to mitigate the risk and frequency of TLS.[191] Initiation and accelerated dose escalation (20–400 mg over 3 weeks) with close inpatient monitoring for TLS can be done in patients with high tumor burden and concern for rapid disease progression on or following BTKi therapy.[178,192,193] 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.

Management of Resistance to Small-Molecule Inhibitors

Acquired resistance to BTKis is predominantly mediated by *BTK* and *PLCG2* mutations.[69,194] *BTK* and/or *PLCG2* mutations were detected at an estimated median of 9 months before relapse in patients treated with ibrutinib, and these mutations were also detected in patients with progressive CLL during ibrutinib therapy up to 15 months before the manifestation of clinical progression.[69,195] *BTK* C481 mutations were also detected in 69% patients with disease relapse at an estimated median of 12 months before relapse in patients treated with acalabrutinib.[194] Long-term follow-up is needed to confirm if *BTK* C481 mutations will emerge in patients treated with zanubrutinib.

Venetoclax is effective for the management of relapsed/refractory CLL after prior treatment with BCRi (ibrutinib or idelalisib),[178-181] although the results of a pooled analysis from four clinical trials showed that BCRi-refractory CLL was significantly associated with lower CR rate and shorter duration of response.[196] Results from other retrospective analyses suggest that the use of venetoclax is associated with higher ORR and improved PFS following failure of ibrutinib (compared to failure of idelalisib) and also in patients who had received only one BCRi (compared to those who had received >1 BCRi).[197,198]

Acquisition of *BCL2* mutations (G101V and D103Y) were implicated in resistance to venetoclax.[199,200] *BCL2* G101V mutation (low variant allele frequency [VAF]) was identified in patients with progressive CLL during venetoclax therapy up to 25 months before clinical progression.[199] Limited available data suggest that subsequent BTKi therapy or retreatment with venetoclax-based regimens is effective in patients with relapsed CLL following treatment with venetoclax, whereas PI3Ki following venetoclax does not appear to result in durable remissions.[201-205]

Testing for *BTK* mutations may be helpful to confirm resistance to BTKis. The reported VAF are variable, with low VAF often associated with disease progression on ibrutinib, leading to speculation that these mutations do not fully explain clinical resistance.[69,195] Testing for *BTK* or *BCL2* mutations as screening for resistance to BTKi or venetoclax is not currently recommended. Testing for *BTK* and *PLCG2* mutations may be useful in patients with disease progression or no response while on BTKi therapy. *BTK* and *PLCG2* mutation status alone is not an indication to change treatment.

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.[55,206-212]

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 relapsed/refractory CLL after initial purine analogue-based therapy.[213]

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.[214,215]

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.[216,217]

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.[218-220] 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 12 months from diagnosis, although the median survival was significantly better for patients who did not receive prior treatment for CLL (46 vs. 8 months; $P < .001$).[221-223]

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:[224-230]

- Unmutated *IGHV* status
- Stereotyped BCR 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.[230] Richter's transformation has also been reported following treatment with ibrutinib and venetoclax.[231-233] Unlike progressive CLL, Richter's transformation developing after treatment with ibrutinib lacked resistance to *BTK* and *PLCG2* mutations.[232] 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.[233] Further studies are 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.[234]

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.[235-237]

A maximum standardized uptake value (SUVmax) greater than or equal to 10 on PET scan has been shown to be a valid marker to distinguish Richter's transformation from CLL among patients mostly treated with chemotherapy or chemoimmunotherapy.[238] However, PET SUVmax greater than or equal to 10 alone lacks both sensitivity and specificity to distinguish Richter's transformation from CLL in patients who develop Richter's transformation while on ibrutinib.[239,240] 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.[241] 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.[242] 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/SLL can either be clonally related to underlying CLL/SLL (78%) or clonally unrelated to underlying CLL/SLL (22%).[229,243] 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).[229] The majority of patients with Richter's transformation to clonally related DLBCL carry unmutated *IGHV.*[243] 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.[229,243]

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.

Enrollment in a clinical trial is the preferred initial treatment option for Richter's transformation to clonally related (or unknown clonal status) DLBCL. In the absence of a suitable clinical trial, chemoimmunotherapy regimens recommended for DLBCL can be used; however, these regimens typically result in poor responses.[221] The regimens listed below are used at the NCCN Member Institutions based on published data (mostly from single-arm phase I/II studies; Table 4).

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)[244]
- R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin)[245]
- R-hyper-CVAD (rituximab, cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone alternating with methotrexate and cytarabine) [246,247]
- OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab) [248,249]

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.[221] However, the use of these prognostic variables

for selection of therapy for Richter's transformation has not yet been established.

Allogeneic HCT can be considered for patients with disease responding to initial chemoimmunotherapy.[221,250,251] 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; $P = .019$).[221] 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.[250] 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.[250]

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.[252-255] 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.[253] 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.[254]

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 time to treatment failure.[256]

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.[219,220,257] 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.[258-260]

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.[261,262] Patients with heavily pretreated fludarabine-refractory CLL have high susceptibility to developing serious infections.[263]

IVIG is associated with a significant decrease in the occurrence of infections but with no improvement in OS outcome.[264-268] 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.[269] 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.[270,271]

The mRNA-based vaccines have shown safety and efficacy against the SARS-CoV-2 infection (COVID-19) among immunocompetent individuals.[272] Studies that have evaluated the safety and efficacy of these vaccines in patients with hematological malignancies have reported lower seroconversion rates and decreased antibody responses in patients with CLL/SLL, regardless of their treatment status.[273-277] The correlation, if any, between antibody titers against spike protein and the protective immunity in this population has not been established, and the duration of any protection is unknown.[278] Therefore, no recommendations can be made regarding antibody testing or actions based on antibody test results. Furthermore, tests are not available to assess cellular immunity post-COVID-19 vaccination. In the absence of laboratory testing to confirm immune response to vaccination, patients with CLL/SLL who have received COVID-19 vaccines should take precautions recommended for unvaccinated individuals, such as mask wearing, social distancing, and diligent hand hygiene, until additional data are available to further clarify

their risk.[278] See NCCN: Cancer and COVID-19 Vaccination for additional updated general information.

Hepatitis B Virus Reactivation

HBV reactivation has been reported in patients treated with chemotherapy ± immunotherapy agents.[279,280] HBV reactivation has also been reported in patients treated with alemtuzumab, ibrutinib, and idelalisib. 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.[281] Patients receiving IVIG may be HBcAb positive as a consequence of IVIG therapy.[282]

Antiviral prophylaxis and monitoring is recommended in high-risk patients receiving anti-CD20 mAb, alemtuzumab, purine analogs, ibrutinib, and idelalisib. Prophylactic antiviral therapy with entecavir is recommended for patients who are HBsAg positive and undergoing anti-lymphoma therapy. Entecavir is more effective than lamivudine in preventing rituximab-associated HBV reactivation.[283,284] Lamivudine prophylaxis should be avoided due to the risks for the development of resistance. The appropriate duration of prophylaxis remains undefined, but the panel recommended that surveillance and antiviral prophylaxis should be continued for up to 12 months after the completion of treatment.[285]

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.[286] Current practices include the use of prophylactic ganciclovir if CMV viremia is present or the use of ganciclovir if the viral load is found to be increasing during therapy.[287,288] 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.[289,290] 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.[291] 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.[291-294] 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.[291,295] 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.[296] 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.[296]

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine,[297] and splenectomy should be used in steroid-refractory cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias.[298-302] Eltrombopag and romiplostim are FDA-approved for the treatment of thrombocytopenia in patients with ITP that is refractory to steroids, IVIG, and splenectomy and have also been

shown to be effective in the management of CLL-associated ITP that is refractory to standard therapies.[303-307]

PRCA is less common in patients with CLL. PRCA can be managed with corticosteroids, cyclophosphamide, cyclosporine, or anti-thymocyte globulin.[290] Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. In very refractory cases, allogeneic HCT may be necessary. Evaluation of parvovirus B19 is also recommended for all patients with PRCA since patients with evidence of parvovirus B19 infection usually respond well to IVIG.[290]

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.[71] 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).[308] Initiation of lenalidomide at lower doses (5, 10, or 15 mg/day) with subsequent dose escalation by 5 mg up to a maximum of 25 mg/day is associated with an acceptable tolerability profile in patients with relapsed or refractory CLL.[309]

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.[310,311] 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.[312,313]

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.[314] 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. The benefit/risk of continuous versus fixed-duration treatment approach should be carefully evaluated. In addition, the type of prior first-line therapy, duration of remission, and acquired resistance to treatment are also important factors in the selection of treatment for relapsed/refractory CLL/SLL.

Ibrutinib and acalabrutinib ± obinutuzumab are the 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. FCR is the preferred treatment option for patients less than 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, acalabrutinib, zanubrutinib, and venetoclax ± rituximab are the preferred treatment options for second-line and subsequent therapy. Acalabrutinib and zanubrutinib are also effective for the management of patients with ibrutinib intolerance. Venetoclax is effective for the management of relapsed/refractory CLL after prior treatment with BCRi (ibrutinib or idelalisib). Optimal sequencing of therapy is yet to be clarified.

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

Table 1: Phase III Randomized Studies of Small Molecule Inhibitor Therapy for Treatment-Naïve CLL/SLL

This table was last updated: June 3, 2022.

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
ELEVATE-TN[120]	**Acalabrutinib**	179 [del(17p) and/or mutated *TP53,* n = 23]	≥65 years or <65 years with comorbidities (CIRS >6; CrCl <70 mL/min); ECOG PS of ≤2 and adequate hematologic, hepatic, and renal function	48 months	90% (11% CR)	78% (HR: 0.19; *P* < .0001)	88%
	Acalabrutinib + obinutuzumab	179 [del(17p) and/or mutated *TP53,* n = 25]			96% (31% CR)	87% (HR: 0.10; *P* < .0001)	93%
	Chlorambucil + obinutuzumab	177 [del(17p) and/or mutated *TP53,* n = 25]			83% (13% CR)	25%	88%
RESONATE-2[122]	**Ibrutinib**	136	≥65 years (without del17p)	7 years	92% (34% CR)	6.5-year PFS: 61%	6.5-year OS: 78%
	Chlorambucil	133			37%	6.5-year PFS: 9%	NR
Alliance North American Intergroup (A041202)[22,23]	**Ibrutinib**	182	≥65 years	55 months	93% (7% CR)	4-year: 76%	4-year: 85%
	Ibrutinib + rituximab	182			94% (12% CR)	4-year: 76%	4-year: 86%
	Bendamustine + rituximab	183			81% (26% CR)	4-year: 47%	4-year: 84%
E1912 study[125]	**Ibrutinib + rituximab**	354	≤70 years	34 months	96% (17% CR)	3-year: 89%	3-year: 99%
	FCR	175			81% (30% CR)	3-year: 73%	3-year: 92%
FLAIR[126]	**Ibrutinib + rituximab**	386	Median age, 62 years (34% >65 years); patients >75 years or with >20% del17p cells were excluded	53 months	-	Median PFS: Not reached	No difference in OS between the 2 arms (HR: 1.01; *P* = .956)
	FCR	385			-	Median PFS: 67 months	
iLLUMINATE[132]	**Ibrutinib + obinutuzumab**	113	≥65 years or <65 years with comorbidities (CIRS >6; CrCl <70 mL/min)	31 months	88% (20% CR)	Median: Not reached (30-month: 79%)	Median: Not reached (30-month: 86%)
	Chlorambucil + obinutuzumab	116			73% (8% CR)	Median: 19 months (30-month: 31%)	Median: Not reached (30-month: 85%)
SEQUOIA[123] **(without del 17p)**	**Zanubrutinib**	241 (mutated *TP53,* n =15)	≥65 y of age OR unsuitable for treatment with FCR (CIRS >6; CrCl <70 mL/min or a history of severe or multiple infections within 2 years) Median age 70 years	24 months	95% (7% CR)	86% (HR: 0.42; *P* < .0001)	94%
	Bendamustine + rituximab	238 (mutated *TP53,* n =13)			85% (15% CR)	70%	95%
SEQUOIA[142] **(with del 17p)**	**Zanubrutinib** (Non-randomized cohort)	109		18 months	95% (3% CR)	89%	95%
CLL14[118]	**Venetoclax + obinutuzumab**	216 [del(17p), n = 17; deleted or mutated *TP53,* n = 25]	≥65 years with comorbidities (CIRS >6; CrCl <70 mL/min)	40 months	85% (50% CR)	3-year PFS: 82% (HR: 0.31; *P* <. 0001)	Median: Not reached in either arm (HR: 1.03; *P* < 0.92)
	Chlorambucil + obinutuzumab	216 [del(17p), n = 14; deleted or mutated *TP53,* n = 24]			71% (23% CR)	3-year PFS: 50%	

Table 2. Phase III Randomized Studies of Small Molecule Inhibitor Therapy for Relapsed/Refractory CLL/SLL

This table was last updated: June 3, 2022.

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
ASCEND[148]	**Acalabrutinib**	155 [del(17p), n = 28; mutated *TP53,* n =39]	Median age 67–68 years with ECOG PS of ≤2 and adequate hematologic, hepatic, and renal function	36 months	83%	Median PFS: Not reached 36-month PFS: 63% (HR: 0.29; *P* < .0001)	36-month: 80%
	Investigator's choice (Idelalisib + rituximab [IdR] or Bendamustine + rituximab [BR])	155 (IdR, n=119; BR, n =36); [del(17p), n = 21; mutated *TP53,* n =34]			85%	Median PFS: 17 months 36-month PFS: 21%	36-month: 73%
RESONATE[149]	**Ibrutinib**	195 [del(17p), n = 63; mutated *TP53,* n =79]	Median age 67 years	74 months	91% (11% CR)	Median PFS: 44 months 60-month PFS: 40%	Median: 68 months
	Ofatumumab	196 [del(17p), n = 64; mutated *TP53,* n =68]			-	Median PFS: 8 months 60-month PFS: 3%	Median: 65 months
ELEVATE-RR[151]	**Acalabrutinib**	268	≥18 years; ECOG PS of ≤2 and the presence of del(17p) and/or del(11q)	41 months	81% (3% CR)	Median PFS: 38 months (for both treatment arms)	Median: Not reached (in either arm)
	Ibrutinib	265			77% (4% CR)		
ALPINE[155]	**Zanubrutinib**	207 [del(17p) and/or mutated *TP53,* n = 41]	Median age 67 years; ECOG PS ≥1; relapsed/refractory disease ≥1 prior systemic therapy	15 months	78% (2% CR)	12-month:95% (HR: 0.40; *P* = .0007)	12-month: 97%
	Ibrutinib	208 [del(17p) and/or mutated *TP53,* n = 38]			63% (1% CR)	12-month: 84%	12-month: 93%
MURANO[86]	**Venetoclax + rituximab**	194 [del(17p), n = 46; mutated *TP53,* n =48]	≥18 years; ECOG PS 0–1; relapsed/refractory disease requiring therapy and adequate bone marrow, liver, and kidney function	59 months	92% (8% CR)	Median PFS: 54 months (HR: 0.19; *P* < .0001)	5-year OS: 82% (HR: 0.40; *P* < .0001)
	Bendamustine + rituximab	195 [del(17p), n = 46; mutated *TP53,* n =51]			72% (4% CR)	Median PFS: 17 months	5-year OS: 62%
Phase III trial[157]	**Idelalisib + rituximab**	110	CIRS>6, renal insufficiency, and/or poor bone marrow reserve that precluded use of chemoimmunotherapy	18 months	84%	Median: 19 months	Median: 41 months (2-year: 70%)
	Placebo + rituximab	110			16%	Median: 6.5 months	Median: 35 months (2-year: 52%)
DUO[158]	**Duvelisib**	160	Median age 69 years	22 months	74%	Median: 13 months (1-year: 60%)	Median: not evaluable; Estimated 1-year OS rate: 86% for both arms
	Ofatumumab	159			45%	Median: 10 months (1-year: 39%)	

Table 3. Adverse Events of BTKis

This table was last updated: June 3, 2022.

Adverse Events	Treatment Naïve CLL			Relapsed/Refractory CLL			
	ELEVATE-TN[120]	RESONATE-2[121]	SEQUOIA[142]	ELEVATE-RR[151]		ALPINE[155]	
	Acalabrutinib	Ibrutinib	Zanubrutinib	Acalabrutinib	Ibrutinib	Zanubrutinib	Ibrutinib
Most common adverse events (all grades)							
Diarrhea	40%	50%	16%	35%	46%	17%	19%
Headache	38%	-	8%	35%	20%	NR	NR
Cough	22%	36%	NR	29%	21%	13%	6%
Fatigue	22%	36%	10%	20%	17%	-	-
Arthralgia	20%	26%	11%	16%	23%	9%	14%
Anemia	-	26%	4%	22%	19%	13%	15%
Neutropenia	12%	13% (Grade ≥3)	18%	21%	25%	28%	22%
Adverse events of special interest (AESI)							
Atrial fibrillation/Flutter							
Any grade	6%	16%	3%	9%	16%	2.5%	10%
Grade ≥3	1%	5%	<1%	5%	3%	1%	2%
Bleeding							
Any grade	42%	NR	45%	38%	51%	36%	36%
Grade ≥3	3%	NR	4%	-	-	3%	3%
Major Bleeding							
Any grade	4%	11%	5%	-	-	3%	4%
Grade ≥3	3%	7%	4%	-	-	3%	3%
Hypertension							
Any grade	7%	23%	14%	9%	23%	17%	16%
Grade ≥3	3%	8%	6%	4%	9%	11%	11%
Infections							
Any grade	74%	26%	62%	-	-	60%	63%
Grade ≥3	16%	-	16%	-	-	13%	18%

Table 4: Chemoimmunotherapy for Richter's Transformation

This table was last updated: June 3, 2022.

Regimen	No. of Patients	Median Follow-up	ORR	Median PFS	OS
RCHOP[244]	15	69 months	67% (7% CR)	10 months	Median: 21 months
REPOCH[245]	46	39 months	39%	4 months	Median: 6 months
R-hyperCVAD[247]	30	8 months	43% (27% CR)	-	1-year OS rate: 28%
OFAR[248]	20	9 months	50%	-	6-month OS rate: 53%
Modified OFAR[249]	35	26 months	39% (7% CR)	-	Median: 7 months 2-year OS rate: 20%

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35020204.

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: https://www.ncbi.nlm.nih.gov/pubmed/17925562.

3. PubMed Overview. Accessed on May 16, 2022. . Available at: https://pubmed.ncbi.nlm.nih.gov/about/.

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

5. 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. Available at: https://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: https://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: https://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: https://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: https://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: https://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: https://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: https://www.ncbi.nlm.nih.gov/pubmed/20511662.

14. 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.

15. 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.

16. 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: https://www.ncbi.nlm.nih.gov/pubmed/27216274.

17. 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: https://www.ncbi.nlm.nih.gov/pubmed/11136261.

18. 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: https://www.ncbi.nlm.nih.gov/pubmed/19117034.

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: https://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: https://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: https://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. Long-term results of Alliance A041202 show continued advantage of ibrutinib-based regimens compared with bendamustine plus rituximab (BR) chemoimmunotherapy [abstract]. Blood 2021;138:Abstract 639. Available at: https://doi.org/10.1182/blood-2021-153146.

24. 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: https://www.ncbi.nlm.nih.gov/pubmed/17666364.

25. 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.

26. 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.

27. 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: https://www.ncbi.nlm.nih.gov/pubmed/21321292.

28. 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: https://www.ncbi.nlm.nih.gov/pubmed/24516016.

29. 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.

30. 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: https://www.ncbi.nlm.nih.gov/pubmed/27109509.

31. 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.

32. 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.

33. 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: https://www.ncbi.nlm.nih.gov/pubmed/11675331.

34. 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: https://www.ncbi.nlm.nih.gov/pubmed/11418478.

35. 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: https://www.ncbi.nlm.nih.gov/pubmed/16098069.

36. 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.

37. 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: https://www.ncbi.nlm.nih.gov/pubmed/12595313.

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

39. 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.

40. 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: https://www.ncbi.nlm.nih.gov/pubmed/16601244.

41. 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: https://www.ncbi.nlm.nih.gov/pubmed/18577710.

42. 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: https://www.ncbi.nlm.nih.gov/pubmed/16079107.

43. 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: https://www.ncbi.nlm.nih.gov/pubmed/22564988.

44. 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: https://www.ncbi.nlm.nih.gov/pubmed/24868078.

45. 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: https://www.ncbi.nlm.nih.gov/pubmed/19224852.

46. 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.

47. 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: https://www.ncbi.nlm.nih.gov/pubmed/17299097.

48. 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: https://www.ncbi.nlm.nih.gov/pubmed/19090008.

49. 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: https://www.ncbi.nlm.nih.gov/pubmed/19903673.

50. 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: https://www.ncbi.nlm.nih.gov/pubmed/21969505.

51. 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.

52. 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.

53. 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.

54. Condoluci A, Terzi di Bergamo L, Langerbeins P, et al. International prognostic score for asymptomatic early-stage chronic lymphocytic leukemia. Blood 2020;135:1859-1869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32267500.

55. 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.

56. 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: https://www.ncbi.nlm.nih.gov/pubmed/23821658.

57. 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: https://www.ncbi.nlm.nih.gov/pubmed/24550227.

58. Nadeu F, Delgado J, Royo C, et al. Clinical impact of clonal and subclonal TP53, SF3B1, BIRC3, NOTCH1, and ATM mutations in chronic lymphocytic leukemia. Blood 2016;127:2122-2130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26837699.

59. Blakemore SJ, Clifford R, Parker H, et al. Clinical significance of TP53, BIRC3, ATM and MAPK-ERK genes in chronic lymphocytic leukaemia:

data from the randomised UK LRF CLL4 trial. Leukemia 2020;34:1760-1774. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32015491.

60. Tausch E, Beck P, Schlenk RF, et al. Prognostic and predictive role of gene mutations in chronic lymphocytic leukemia: results from the pivotal phase III study COMPLEMENT1. Haematologica 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31919090.

61. 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: https://www.ncbi.nlm.nih.gov/pubmed/23243274.

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. Ahn IE, Tian X, Ipe D, et al. Prediction of outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: Development and validation of a four-factor prognostic model. J Clin Oncol 2021;39:576-585. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33026937.

64. Soumerai JD, Ni A, Darif M, et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukaemia treated with targeted therapies or chemoimmunotherapy: a retrospective, pooled cohort study with external validations. Lancet Haematol 2019;6:e366-e374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31109827.

65. 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.

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. BTK(C481S)-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. 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.

71. 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: https://www.ncbi.nlm.nih.gov/pubmed/21523725.

72. 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: https://www.ncbi.nlm.nih.gov/pubmed/24415539.

73. 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: https://www.ncbi.nlm.nih.gov/pubmed/22778323.

74. 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.

75. 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.

76. 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.

77. Thompson PA, Srivastava J, Peterson C, et al. Minimal residual disease undetectable by next-generation sequencing predicts improved outcome in CLL after chemoimmunotherapy. Blood 2019;134:1951-1959. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31537528.

78. 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.

79. Raponi S, Della Starza I, De Propris MS, et al. Minimal residual disease monitoring in chronic lymphocytic leukaemia patients. A comparative analysis of flow cytometry and ASO IgH RQ-PCR. Br J Haematol 2014;166:360-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24735016.

80. Rawstron AC, Kreuzer KA, Soosapilla A, et al. Reproducible diagnosis of chronic lymphocytic leukemia by flow cytometry: An European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation project. Cytometry B Clin Cytom 2018;94:121-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29024461.

81. Wierda WG, Rawstron A, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. Leukemia 2021;35:3059-3072. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34168283.

82. 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.

83. 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.

84. Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: Extended off-treatment follow-up from the randomized CLL14 study. J Clin Oncol 2021;39:4049-4060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34709929.

85. 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.

86. Kater AP, Kipps TJ, Eichhorst B, et al. Five-year analysis of murano study demonstrates enduring undetectable minimal residual disease (uMRD) in a subset of relapsed/refractory chronic lymphocytic leukemia (R/R CLL) patients (Pts) following fixed-duration venetoclax-rituximab

(VenR) therapy (Tx) [abstract]. Blood 2020;136:19-21. Available at: https://doi.org/10.1182/blood-2020-136109.

87. Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO Phase III Study. J Clin Oncol 2020;38:4042-4054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32986498.

88. Eichhorst B, Niemann C, Kater AP, et al. A randomized phase III study of venetoclax-based time-limited combination treatments (RVe, GVe, GIVe) vs standard chemoimmunotherapy (CIT: FCR/BR) in frontline chronic lymphocytic leukemia (CLL) of fit patients: first co-primary endpoint analysis of the International Intergroup GAIA (CLL13) Trial [abstract]. Blood 2021;138:Abstract 71. Available at: https://doi.org/10.1182/blood-2021-146161.

89. Wierda WG, Allan JN, Siddiqi T, et al. Ibrutinib plus venetoclax for first-line treatment of chronic lymphocytic leukemia: Primary analysis results from the minimal residual disease cohort of the randomized phase II CAPTIVATE Study. J Clin Oncol 2021;39:3853-3865. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34618601.

90. Ghia P, Allan JN, Siddiqi T, et al. First-line treatment with ibrutinib (Ibr) plus venetoclax (Ven) for chronic lymphocytic leukemia (CLL): 2-year post-randomization disease-free survival (DFS) results from the minimal residual disease (MRD) cohort of the phase 2 Captivate study [abstract]. Blood 2021;138:Abstract 68. Available at: https://doi.org/10.1182/blood-2021-144544.

91. Munir T, Moreno C, Owen C, et al. First prospective data on minimal residual disease (MRD) outcomes after fixed-duration ibrutinib plus venetoclax (Ibr+Ven) versus chlorambucil plus obinutuzumab (Clb+O) for first-line treatment of CLL in elderly or unfit patients: The Glow Study [abstract]. Blood 2021;138:Abstract 70. Available at: https://doi.org/10.1182/blood-2021-148666.

92. Biosimilar and Interchangeable Products. Available at: https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products.

93. Biosimilar Development, Review, and Approval. Available at: https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval.

94. 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: https://www.ncbi.nlm.nih.gov/pubmed/20595513.

95. 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.

96. 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.

97. 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: https://www.ncbi.nlm.nih.gov/pubmed/25713417.

98. 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: https://www.ncbi.nlm.nih.gov/pubmed/16840733.

99. 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: https://www.ncbi.nlm.nih.gov/pubmed/21156225.

100. 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.

101. 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.

102. 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.

103. 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.

104. 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: https://www.ncbi.nlm.nih.gov/pubmed/11807008.

105. 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: https://www.ncbi.nlm.nih.gov/pubmed/18687638.

106. 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.

107. 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.

108. 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.

109. 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.

110. 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.

111. 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.

112. 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: https://www.ncbi.nlm.nih.gov/pubmed/24286263.

113. 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: https://www.ncbi.nlm.nih.gov/pubmed/24615780.

114. Herling CD, Cymbalista F, Gross-Ophoff-Muller C, et al. Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial. Leukemia 2020;34:2038-2050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32071431.

115. 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.

116. 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: https://www.ncbi.nlm.nih.gov/pubmed/24584349.

117. 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: https://www.ncbi.nlm.nih.gov/pubmed/18811613.

118. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020;21:1188-1200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32888452.

119. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet 2020;395:1278-1291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32305093.

120. Sharman JP, Egyed M, Jurczak W, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naive chronic lymphocytic leukemia. Leukemia 2022;36:1171-1175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34974526.

121. 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 2020;34:787-798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31628428.

122. Barr PM, Owen C, Robak T, et al. Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia [abstract]. J Clin Oncol 2021;39:Abstract 7523. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.7523.

123. Tam CS, Giannopoulos K, Jurczak W, et al. SEQUOIA: Results of a phase 3 randomized study of zanubrutinib versus bendamustine + rituximab (BR) in patients with treatment-naïve (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [abstract]. Blood 2021;138:Abstract 396. Available at: https://doi.org/10.1182/blood-2021-148457.

124. 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.

125. 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.

126. Hillmen P, Pitchford A, Bloor A, et al. Ibrutinib plus rituximab is superior to FCR in previously untreated CLL: Results of the phase III NCRI FLAIR trial [abstract]. Blood 2021;138:Abstract 642. Available at: https://doi.org/10.1182/blood-2021-152319.

127. Kutsch N, Bahlo J, Robrecht S, et al. Long term follow-up data and health-related quality of life in frontline therapy of fit patients treated with FCR versus BR (CLL10 trial of the GCLLSG). Hemasphere 2020;4:e336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32072150.

128. 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.

129. Sharman JP, Burke JM, Yimer HA, et al. Phase 2, multicenter GIBB study of obinutuzumab plus bendamustine in previously untreated patients with chronic lymphocytic leukemia. Leuk Lymphoma 2021;62:791-800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33243049.

130. Stilgenbauer S, Bosch F, Ilhan O, et al. Safety and efficacy of obinutuzumab alone or with chemotherapy in previously untreated or relapsed/refractory chronic lymphocytic leukaemia patients: Final analysis of the Phase IIIb GREEN study. Br J Haematol 2021;193:325-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33605445.

131. 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.

132. 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.

133. 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: https://www.ncbi.nlm.nih.gov/pubmed/18710390.

134. 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 2011;117:2452-2460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24048793.

135. 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: https://www.ncbi.nlm.nih.gov/pubmed/15051774.

136. 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: https://www.ncbi.nlm.nih.gov/pubmed/19693094.

137. 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.

138. 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.

139. 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: https://www.ncbi.nlm.nih.gov/pubmed/12721250.

140. 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.

141. 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.

142. Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. Haematologica 2020;106:2354-2363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33054121.

143. 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: https://www.ncbi.nlm.nih.gov/pubmed/12130484.

144. 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: https://www.ncbi.nlm.nih.gov/pubmed/17984186.

145. 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.

146. 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.

147. Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2020;38:2849-2861. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459600.

148. Jurczak W, Pluta A, Wach M, et al. Three-year follow-up of the Ascend trial: Acalabrutinib vs rituximab plus idelalisib or bendamustine in relapsed/refractory chronic lymphocytic leukemia [abstract]. Blood 2021;138:Abstract 393. Available at: https://doi.org/10.1182/blood-2021-146570.

149. 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;94:1353-1363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31512258.

150. 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.

151. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: Results of the first randomized phase III trial. J Clin Oncol 2021;39:3441-3452. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34310172.

152. 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.

153. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood 2019;134:851-859. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31340982.

154. Xu W, Yang S, Zhou K, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study. J Hematol Oncol 2020;13:48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32393328.

155. Hillmen P, Eichhorst B, Brown JR, et al. First interim analysis of ALPINE study: results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. EHA Virtual Congress; 2021:Abstract LB1900. Available at:

156. 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.

157. 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.

158. 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.

159. Davids MS, Kuss BJ, Hillmen P, et al. Efficacy and safety of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL or SLL in the DUO Crossover Extension Study. Clin Cancer Res 2020;26:2096-2103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31964785.

160. 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.

161. 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: https://www.ncbi.nlm.nih.gov/pubmed/24615777.

162. 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.

163. 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: https://www.ncbi.nlm.nih.gov/pubmed/20194844.

164. 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: https://www.ncbi.nlm.nih.gov/pubmed/21245487.

165. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21844497.

166. Fraser GAM, Chanan-Khan A, Demirkan F, et al. Final 5-year findings from the phase 3 HELIOS study of ibrutinib plus bendamustine and rituximab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Leuk Lymphoma 2020;61:3188-3197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32762271.

167. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27731748.

168. 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: https://www.ncbi.nlm.nih.gov/pubmed/18754025.

169. 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.

170. 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: https://www.ncbi.nlm.nih.gov/pubmed/23270003.

171. 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: https://www.ncbi.nlm.nih.gov/pubmed/26967821.

172. 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.

173. 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.

174. 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: https://www.ncbi.nlm.nih.gov/pubmed/11986207.

175. 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: https://www.ncbi.nlm.nih.gov/pubmed/24292560.

176. 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.

177. 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: https://www.ncbi.nlm.nih.gov/pubmed/19597025.

178. 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.

179. 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.

180. Eyre TA, Kirkwood AA, Gohill S, et al. Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. Br J Haematol 2019;185:656-669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30768675.

181. Innocenti I, Morelli F, Autore F, et al. Venetoclax in CLL patients who progress after B-cell Receptor inhibitor treatment: a retrospective multi-centre Italian experience. Br J Haematol 2019;187:e8-e11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31364153.

182. 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.

183. 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.

184. 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.

185. Shadman M, Sharman JP, Levy MY, et al. Phase 2 study of zanubrutinib in patients with relapsed/refractory B-cell malignancies intolerant to ibrutinib/acalabrutinib [abstract]. Blood 2020;136:51-52. Available at: https://doi.org/10.1182/blood-2020-134621.

186. Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. Haematologica 2021;106:2364-2373. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33730844.

187. 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.

188. 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.

189. 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.

190. 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.

191. 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.

192. 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.

193. Koenig KL, Huang Y, Dotson EK, et al. Safety of venetoclax rapid dose escalation in CLL patients previously treated with B-cell receptor signaling antagonists. Blood Adv 2020;4:4860-4863. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031541.

194. Byrd JC, Jones D, Lozanski G, 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.

195. 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.

196. Roberts AW, Ma S, Kipps TJ, et al. Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. Blood 2019;134:111-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31023700.

197. 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.

198. 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.

199. Blombery P, Anderson MA, Gong JN, et al. Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. Cancer Discov 2019;9:342-353. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30514704.

200. Tausch E, Close W, Dolnik A, et al. Venetoclax resistance and acquired BCL2 mutations in chronic lymphocytic leukemia. Haematologica 2019;104:e434-e437. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31004028.

201. Brown JR, Davids MS, Chang JE, et al. Outcomes of ibrutinib (Ibr) therapy in Ibr-naïve patients (pts) with chronic lymphocytic leukemia (CLL) progressing after venetoclax (Ven) [abstract]. Blood 2019;134:Abstract 4320. Available at: https://doi.org/10.1182/blood-2019-123665.

202. Lin VS, Lew TE, Handunnetti SM, et al. BTK inhibitor therapy is effective in patients with CLL resistant to venetoclax. Blood 2020;135:2266-2270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32244251.

203. Mato AR, Roeker LE, Jacobs R, et al. Assessment of the efficacy of therapies following venetoclax discontinuation in CLL reveals BTK inhibition as an effective strategy. Clin Cancer Res 2020;26:3589-3596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32198151.

204. Harrup RA, Owen C, D'Rozario J, et al. Efficacy of subsequent novel targeted therapies, including repeated venetoclax-rituximab (VenR), in patients (Pts) with relapsed/refractory chronic lymphocytic leukemia (R/R CLL) previously treated with fixed-duration VenR in the Murano study [abstract]. Blood 2020;136:44-45. Available at: https://doi.org/10.1182/blood-2020-137415.

205. Thompson MC, Allan JN, Sail K, et al. Venetoclax re-treatment of chronic lymphocytic leukemia (CLL) patients after a previous venetoclax-based regimen [abstract]. Blood 2020;136:39-41. Available at: https://doi.org/10.1182/blood-2020-138725.

206. 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: https://www.ncbi.nlm.nih.gov/pubmed/15809449.

207. 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: https://www.ncbi.nlm.nih.gov/pubmed/18711173.

208. 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: https://www.ncbi.nlm.nih.gov/pubmed/18794548.

209. 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.

210. 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.

211. 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.

212. 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.

213. 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.

214. 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.

215. 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.

216. 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.

217. Kim HT, Ahn KW, Hu ZH, et al. Prognostic score and cytogenetic risk classification for chronic lymphocytic leukemia patients: Center for International Blood and Marrow Transplant Research Report. Clin Cancer Res 2019;25:5143-5155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31253630.

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

219. 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: https://www.ncbi.nlm.nih.gov/pubmed/16902984.

220. 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.

221. 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: https://www.ncbi.nlm.nih.gov/pubmed/16710033.

222. Al-Sawaf O, Robrecht S, Bahlo J, et al. Richter transformation in chronic lymphocytic leukemia (CLL)-a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. Leukemia 2021;35:169-176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32203141.

223. Wang Y, Tschautscher MA, Rabe KG, et al. Clinical characteristics and outcomes of Richter transformation: experience of 204 patients from a single center. Haematologica 2020;105:765-773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31197071.

224. 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.

225. 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: https://www.ncbi.nlm.nih.gov/pubmed/22571487.

226. 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: https://www.ncbi.nlm.nih.gov/pubmed/23295735.

227. 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: https://www.ncbi.nlm.nih.gov/pubmed/24004666.

228. 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: https://www.ncbi.nlm.nih.gov/pubmed/24127483.

229. 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.

230. 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.

231. 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.

232. 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.

233. 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.

234. 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: https://www.ncbi.nlm.nih.gov/pubmed/20421272.

235. 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.

236. 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.

237. 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.

238. 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.

239. Mato AR, Wierda WG, Davids MS, et al. Utility of positron emission tomography-computed tomography in patients with chronic lymphocytic leukemia following B-cell receptor pathway inhibitor therapy.

Haematologica 2019;104:2258-2264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30923097.

240. Wang Y, Rabe KG, Bold MS, et al. The role of 18F-FDG-PET in detecting Richter's transformation of chronic lymphocytic leukemia in patients receiving therapy with a B-cell receptor inhibitor. Haematologica 2020;105:240564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31974193.

241. 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.

242. 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.

243. 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.

244. 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.

245. 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.

246. 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.

247. 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: https://www.ncbi.nlm.nih.gov/pubmed/12655528.

248. 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: https://www.ncbi.nlm.nih.gov/pubmed/18182662.

249. 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: https://www.ncbi.nlm.nih.gov/pubmed/23810245.

250. 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: https://www.ncbi.nlm.nih.gov/pubmed/22547610.

251. 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.

252. 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.

253. 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.

254. 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.

255. Armand P, Murawski N, Molin D, et al. Pembrolizumab in relapsed or refractory Richter syndrome. Br J Haematol 2020;190:e117-e120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32544980.

256. 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.

257. 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: https://www.ncbi.nlm.nih.gov/pubmed/24511013.

258. 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.

259. 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.

260. Stephens DM, Boucher K, Kander E, et al. Hodgkin lymphoma arising in patients with chronic lymphocytic leukemia: outcomes from a large multi-center collaboration. Haematologica 2021;106:2845-2852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33054118.

261. 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: https://www.ncbi.nlm.nih.gov/pubmed/19828698.

262. 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: https://www.ncbi.nlm.nih.gov/pubmed/20620978.

263. 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: implications for clinical trials in this patient population. Cancer 2002;94:2033-2039. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11932906.

264. 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: https://www.ncbi.nlm.nih.gov/pubmed/7803248.

265. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic L, Gale RP, Chapel HM, et al. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. N Engl J Med 1988;319:902-907. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2901668.

266. 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: https://www.ncbi.nlm.nih.gov/pubmed/7621634.

267. 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: https://www.ncbi.nlm.nih.gov/pubmed/8641639.

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

269. Kim DK, Bridges CB, Harriman KH, et al. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older--United States, 2015. MMWR Morb Mortal Wkly Rep 2015;64:91-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25654609.

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

271. Mauro FR, Giannarelli D, Galluzzo CM, et al. Response to the conjugate pneumococcal vaccine (PCV13) in patients with chronic lymphocytic leukemia (CLL). Leukemia 2021;35:737-746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32555297.

272. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 Vaccines. JAMA 2021;325:1318-1320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33635317.

273. Bergman P, Blennow O, Hansson L, et al. Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial. EBioMedicine 2021;74:103705. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34861491.

274. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021;137:3165-3173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33861303.

275. Parry H, McIlroy G, Bruton R, et al. Antibody responses after first and second Covid-19 vaccination in patients with chronic lymphocytic leukaemia. Blood Cancer J 2021;11:136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34330895.

276. Haggenburg S, Lissenberg-Witte BI, van Binnendijk RS, et al. Quantitative analysis of mRNA-1273 COVID-19 vaccination response in immunocompromised adult hematology patients. Blood Adv 2022;6:1537-1546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35114690.

277. Herishanu Y, Rahav G, Levi S, et al. Efficacy of a third BNT162b2 mRNA COVID-19 vaccine dose in patients with CLL who failed standard 2-dose vaccination. Blood 2022;139:678-685. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34861036.

278. Diefenbach C, Caro J, Koide A, et al. Impaired Humoral Immunity to SARS-CoV-2 Vaccination in Non-Hodgkin Lymphoma and CLL Patients. medRxiv 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34100025.

279. 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: https://www.ncbi.nlm.nih.gov/pubmed/11055239.

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

281. 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.

282. 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: https://www.ncbi.nlm.nih.gov/pubmed/20576011.

283. 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: https://www.ncbi.nlm.nih.gov/pubmed/23775967.

284. 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: https://www.ncbi.nlm.nih.gov/pubmed/23910494.

285. 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: https://www.ncbi.nlm.nih.gov/pubmed/19144986.

286. 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: https://www.ncbi.nlm.nih.gov/pubmed/17026823.

287. 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: https://www.ncbi.nlm.nih.gov/pubmed/15477211.

288. 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: https://www.ncbi.nlm.nih.gov/pubmed/17169798.

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

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

291. 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. Br J Haematol 2007;136:800-805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17341265.

292. 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.

293. 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.

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

295. 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: https://www.ncbi.nlm.nih.gov/pubmed/18055869.

296. 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: https://www.ncbi.nlm.nih.gov/pubmed/17986663.

297. 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: https://www.ncbi.nlm.nih.gov/pubmed/11596014.

298. 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: https://www.ncbi.nlm.nih.gov/pubmed/12200396.

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

300. 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: https://www.ncbi.nlm.nih.gov/pubmed/12357362.

301. 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: https://www.ncbi.nlm.nih.gov/pubmed/16823816.

302. 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;112:999-1004. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18463354.

303. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:641-648. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19231632.

304. 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: https://www.ncbi.nlm.nih.gov/pubmed/21067381.

305. D'Arena G, Cascavilla N. Romiplostim for chronic lymphocytic leukemia-associated immune thrombocytopenia. Leuk Lymphoma 2011;52:701-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21171868.

306. Sinisalo M, Sankelo M, Itala-Remes M. Thrombopoietin receptor agonists can be used temporarily with patients suffering from refractory chronic lymphocytic leukemia-associated immunologic thrombocytopenia. Leuk Lymphoma 2011;52:724-725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21323511.

307. Paul S, Jain N, Ferrajoli A, et al. A phase II trial of eltrombopag for patients with chronic lymphocytic leukaemia (CLL) and thrombocytopenia. Br J Haematol 2019;185:606-608. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30406944.

308. 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: https://www.ncbi.nlm.nih.gov/pubmed/18427150.

309. 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.

310. 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: https://www.ncbi.nlm.nih.gov/pubmed/18334676.

311. 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: https://www.ncbi.nlm.nih.gov/pubmed/21812019.

312. 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.

313. 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.

314. 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.