

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Hodgkin's Lymphomas

Version 2.2015

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Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

DIAGNOSIS

ESSENTIAL:

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

Absolute monoclonal B lymphocyte count^d

INFORMATIVE FOR PROGNOSTIC AND/OR THERAPY DETERMINATION:^e

- FISH to detect: +12; del(11q); del(13q); del(17p); or stimulated cytogenetics to detect: +12; del(11q); del(13q); del(17p) or complex karyotype
- Molecular analysis to detect: IGHV mutation status
- Determination of CD38 and ZAP-70 expression by flow cytometry, methylation, or immunohistochemistry^f
- TP53 sequencing

^aCLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma. Cases diagnosed as B-PLL are excluded from this guideline.

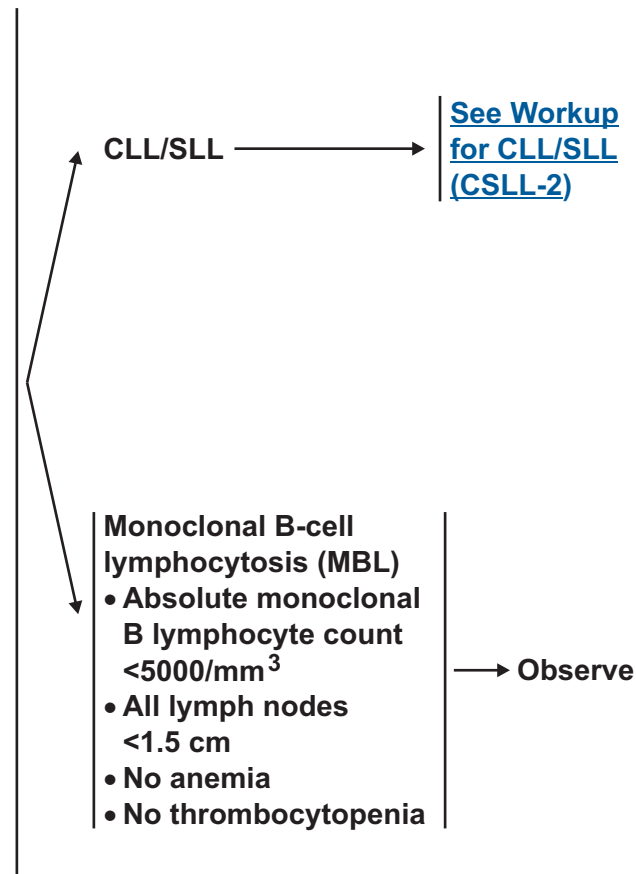
^bTypical immunophenotype: CD5+, CD23+, CD43+/-, CD10-, CD19+, CD20 dim, slg dim+, and cyclin D1-. Note: Some cases may be slg bright+, CD23- or dim, and some MCL may be CD23+; cyclin D1 immunohistochemistry or FISH for t(11;14) should be considered in all cases and should be done in cases with an atypical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

^cSee [Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms \(NHODG-A\)](#).

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

^eSee [Prognostic Information for CLL \(CSLL-A\)](#).

^fEvaluation of ZAP-70 expression can be challenging and ZAP-70 is not recommended outside the setting of a clinical trial. Methylation status is not widely available outside of a clinical trial.



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

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

WORKUP

ESSENTIAL:

- Physical exam: attention to node-bearing areas, including Waldeyer's ring, and to size of liver and spleen
- Performance status
- B symptoms
- CBC, differential, platelets
- Comprehensive metabolic panel
- Hepatitis B testing⁹ if CD20 monoclonal antibody contemplated
- MUGA scan/echocardiogram if anthracycline- or anthracenedione-based regimen is indicated
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct Coombs' test
- Chest/abdominal/pelvic CT should be done prior to initiation of therapy (particularly when peripheral adenopathy is present and symptoms suggest bulky lymph nodes)
- Beta-2-microglobulin
- LDH
- Uric acid
- Unilateral bone marrow biopsy (± aspirate) at initiation of therapy
- Discussion of fertility issues and sperm banking
- PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected

[SLL/Localized
\(Ann Arbor Stage I\)
\(See CSLL-3\)](#)

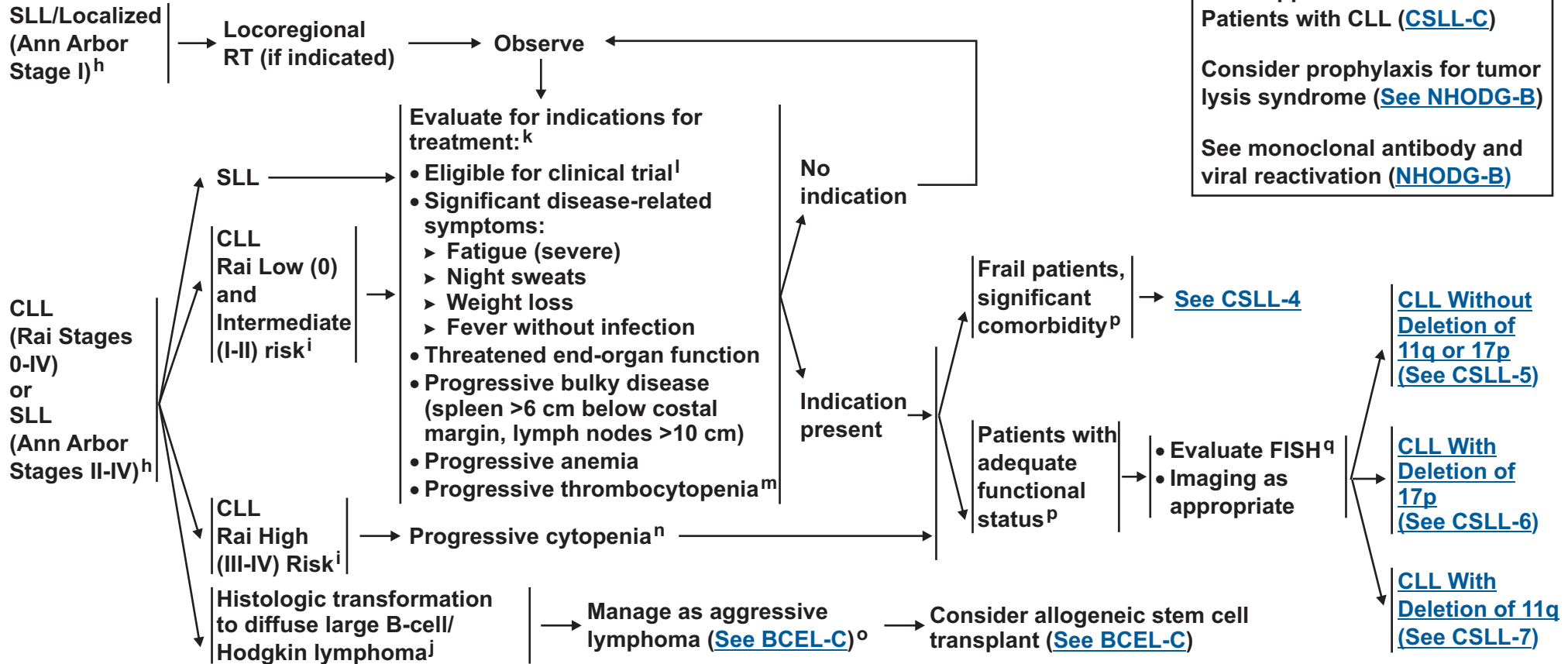
[CLL \(Rai Stages 0–IV\) or
SLL
\(Ann Arbor Stage II–IV\)
\(See CSLL-3\)](#)

⁹Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.

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PRESENTATION



^hSee Supportive Care for Patients with CLL (CSLL-C).

ⁱSee Rai and Binet Classification Systems (CSLL-B).

^jIncreased polymorphocytes in blood (>5%–<55%) (so-called “CLL-PL” or CLL with increased polymorphocytes) as well as the presence of expanded proliferation centers (broader than a 20x field) or a high proliferation rate (either >2.4 mitoses/proliferation center or Ki-67 >40%/proliferation center) on lymph node biopsy (so-called “accelerated CLL”) are associated with more aggressive disease and poorer outcome; neither of these findings is considered to represent Richter’s transformation and optimal management has not been established.

^kAbsolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10⁹/L or symptoms related to leukostasis.

^lGiven incurability with conventional therapy, consider a clinical trial as first line of treatment.

^mPlatelet counts >100,000 cells/mm³ are typically not associated with clinical risk.

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

^oIn addition to the regimens listed in BCEL-C, R-HyperCVAD has also been used in this setting.

^pSalvi 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.

^qRe-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] is necessary to direct treatment.

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FRAIL PATIENTS, SIGNIFICANT COMORBIDITY

FIRST-LINE
THERAPY

RELAPSED/
REFRACTORY
THERAPY

See Supportive Care for
Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor
lysis syndrome ([See NHODG-B](#))

See monoclonal antibody and
viral reactivation ([NHODG-B](#))

Frail patients, significant
comorbidity^p (not able to
tolerate purine analogs)^{h,k,l}

→ See Suggested Regimens
([CSLL-D 1 of 7](#))

→ See Suggested Regimens
([CSLL-D 2 of 7](#))

^hSee [Supportive Care for Patients with CLL \(CSLL-C\)](#).

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CLL WITHOUT DELETION OF 11q or 17p

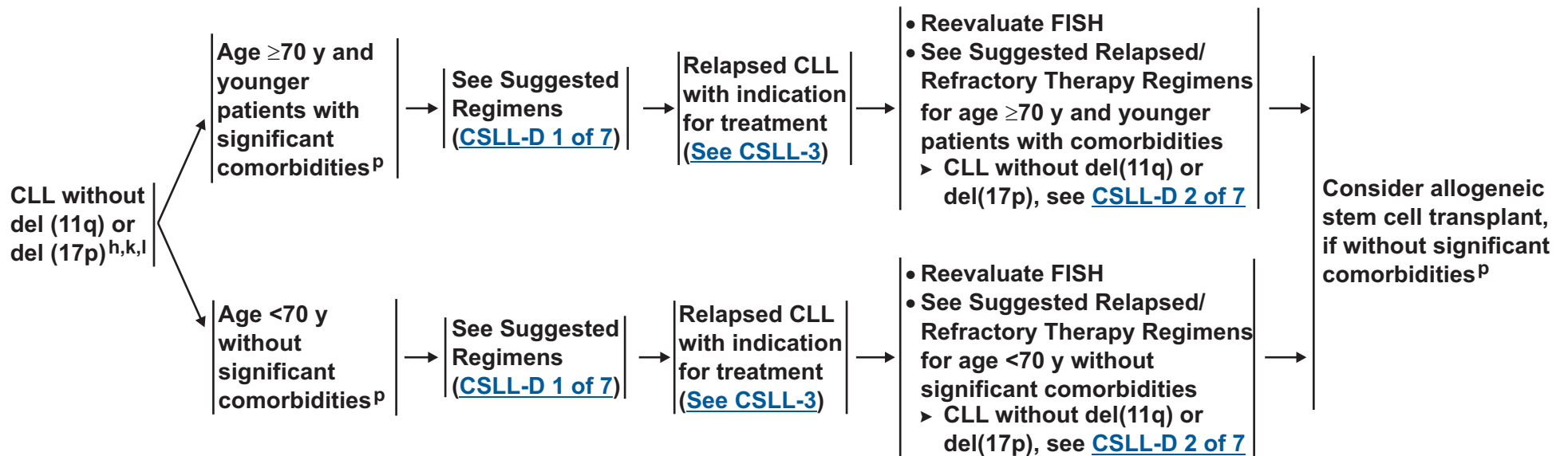
FIRST-LINE
THERAPY

RELAPSED/
REFRACTORY
THERAPY

See Supportive Care for
Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor
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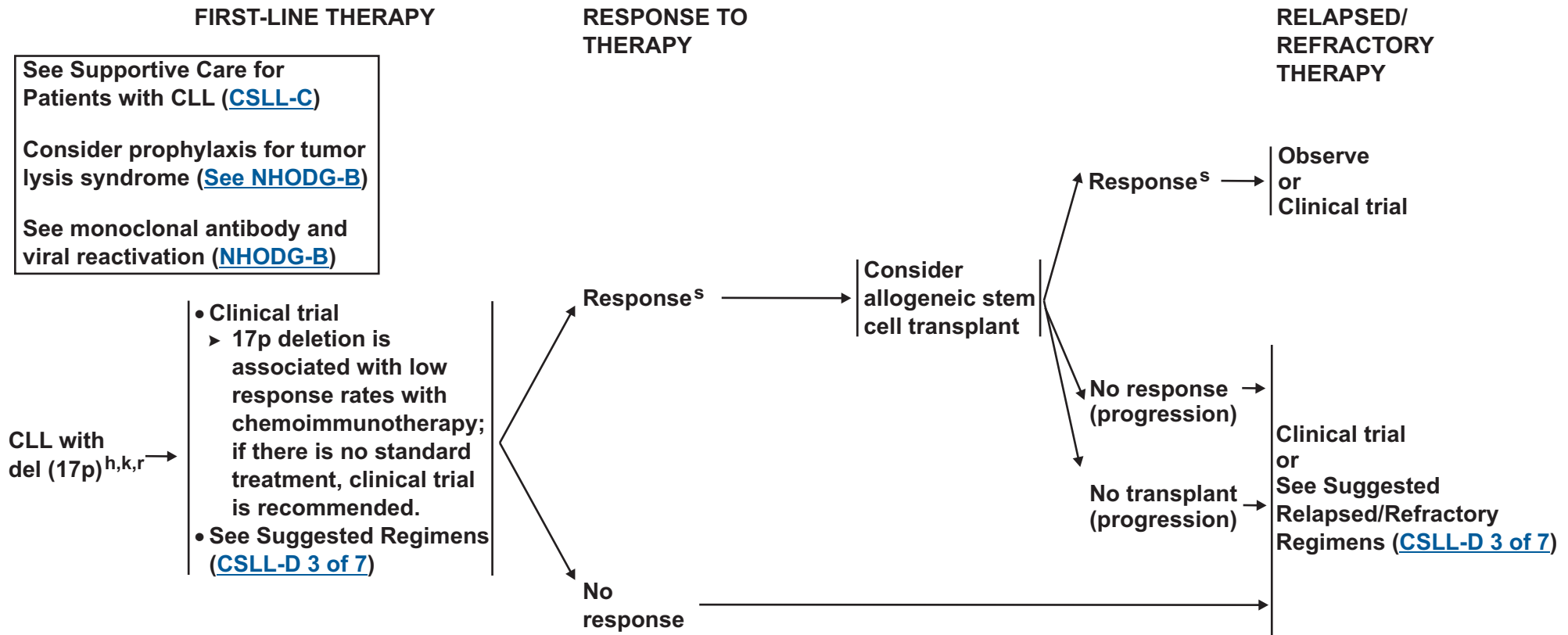
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^pSalvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc* 2008;56:1926-1931.

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CLL WITH DELETION OF 17p



^hSee [Supportive Care for Patients with CLL \(CSLL-C\)](#).

^kAbsolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10⁹/L or symptoms related to leukostasis.

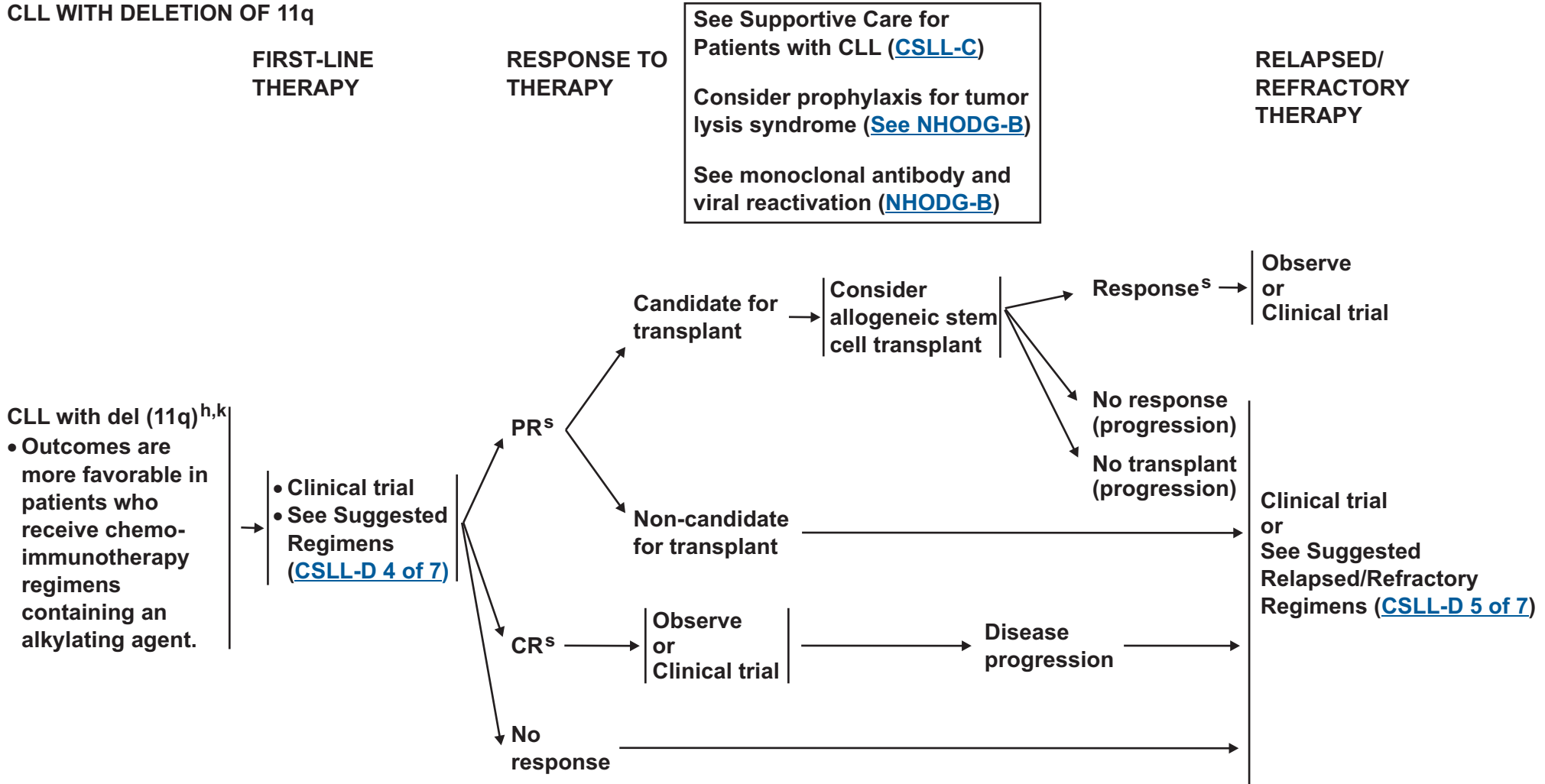
^rPatients with low positivity should be retested due to chance of false-positive results.

^sSee [Response Criteria: CLL \(CSLL-E\)](#) or [SLL \(NHODG-C\)](#).

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CLL WITH DELETION OF 11q



^hSee [Supportive Care for Patients with CLL \(CSLL-C\)](#).

^kAbsolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10⁹/L or symptoms related to leukostasis.

^sSee [Response Criteria: CLL \(CSLL-E\)](#) or [SLL \(NHODG-C\)](#).

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PROGNOSTIC INFORMATION FOR CLL^a

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

	Outcome Association	
	Favorable	Unfavorable
DNA sequencing^b IGHV	>2% mutation	≤2% mutation
Flow Cytometry CD38 Zap 70	<30% <20%	≥30% ≥20%

Interphase Cytogenetics (FISH)^c

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

Complex karyotype^d

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

^aThis table provides useful prognostic information relative to the time to progression where therapy is required and survival. The presence of del(11q) and/or del(17p) are associated with short progression-free survival to chemotherapy and chemoimmunotherapy approaches. Alemtuzumab or high-dose steroids have response in del(17p) disease.

^bIGHV rearrangements involving VH3-21 carry a poor prognosis even if mutated.

^cFormal 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.

^dComplex karyotype is based on results of conventional karyotyping of stimulated CLL cells.

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CLL STAGING SYSTEMS

Rai System^a

Stage	Description	Risk Status
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0–I with splenomegaly, hepatomegaly, or both	Intermediate
III ^c	Stage 0–II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV ^c	Stage 0–III with platelets <100,000/mcL	High

Binet System^b

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

^aThis research was originally published in Blood. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46(2):219-234. (c) The American Society of Hematology.

^bFrom: 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.

^cImmune-mediated cytopenias are not the basis for these stage definitions.

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SUPPORTIVE CARE FOR PATIENTS WITH CLL

Recurrent Sinopulmonary Infections (requiring IV antibiotics or hospitalization)	<ul style="list-style-type: none"> • Antimicrobials as appropriate • Evaluate serum IgG, if <500 mg/dL <ul style="list-style-type: none"> ➢ begin monthly IVIG 0.3–0.5 g/kg, ➢ adjust dose/interval to maintain nadir level of approximately 500 mg/dL
Antiinfective Prophylaxis	<ul style="list-style-type: none"> • Recommended for patients receiving purine-analog and/or alemtuzumab during treatment and thereafter, if tolerated <ul style="list-style-type: none"> ➢ Herpes virus (acyclovir or equivalent) ➢ PCP (sulfamethoxazole/trimethoprim or equivalent) • Alemtuzumab: Clinicians must be aware of the high risk of CMV reactivation. The current appropriate management is controversial; some use ganciclovir (oral or IV) prophylactically if viremia is present, others use ganciclovir only if viral load is rising. CMV viremia should be measured by PCR quantitation at least every 2–3 wks. Consultation with an infectious disease expert may be necessary. • Recommend HBV prophylaxis and monitoring in high-risk patients receiving anti-CD20 monoclonal antibodies and alemtuzumab. See Supportive Care for NHL (NHODG-B) for details on the management of infections.
Autoimmune Cytopenias	<ul style="list-style-type: none"> • Autoimmune hemolytic anemia (AIHA): Diagnosis with reticulocyte count, haptoglobin, DAT <ul style="list-style-type: none"> ➢ AIHA that develops in setting of treatment with fludarabine: stop, treat, and avoid subsequent fludarabine • Immune thrombocytopenic purpura (ITP): Evaluate bone marrow for cause of low platelets • Pure red cell aplasia (PRCA): Evaluate for parvo B19 and bone marrow evaluation • Treatment: Corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim (ITP)
Vaccination	<ul style="list-style-type: none"> • Annual influenza vaccine^a • Pneumococcal vaccine (Prevnar preferred) every 5 yrs • Avoid all live vaccines, including Zoster
Blood Product Support	<ul style="list-style-type: none"> • Transfuse according to institutional or published standards • Irradiate all blood products to avoid transfusion-associated GVHD

^aIn 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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SUPPORTIVE CARE FOR PATIENTS WITH CLL

Tumor Lysis Syndrome (TLS)	<ul style="list-style-type: none"> • Consider tumor prophylaxis measures in patients with bulky disease at high risk for TLS. <ul style="list-style-type: none"> ➢ For details on the symptoms, prophylaxis, and management of TLS in NHL, see Supportive Care for NHL (NHODG-B).
Tumor Flare Reactions	<ul style="list-style-type: none"> • Management of tumor flare recommended for patients receiving lenalidomide • Tumor flare reactions: <ul style="list-style-type: none"> ➢ 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: <ul style="list-style-type: none"> ➢ Steroids (eg, prednisone 25–50 mg PO for 5–10 days) ➢ Antihistamines for rash and pruritus (cetirizine 10 mg PO QID or loratadine 10 mg PO daily) • Prophylaxis: <ul style="list-style-type: none"> ➢ Consider in patients with bulky lymph nodes (>5 cm) ➢ Steroids (eg, prednisone 20 mg PO for 5–7 days followed by rapid taper over 5–7 days)
Thromboprophylaxis	<ul style="list-style-type: none"> • Recommended for prevention of thromboembolic events in patients receiving lenalidomide: <ul style="list-style-type: none"> ➢ Aspirin 81 mg daily if platelets above $50 \times 10^{12}/L$ ➢ Patients already on anticoagulants, such as warfarin, do not need aspirin • Note that the above may differ from the NCCN Guidelines for Venous Thromboembolic Disease in which the recommendations with lenalidomide pertain only to patients with multiple myeloma

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SUGGESTED TREATMENT REGIMENS^a (in order of preference)

CLL without del (11q) or del (17p)

Frail patient, significant comorbidity (not able to tolerate purine analogs)

- Obinutuzumab + chlorambucil (category 1)
- Ofatumumab + chlorambucil
- Rituximab + chlorambucil
- Obinutuzumab (category 2B)
- Rituximab (category 2B)
- Chlorambucil (category 2B)
- Pulse corticosteroids (category 3)

First-line therapy^b

- Age ≥70 y and younger patients with significant comorbidities
 - Obinutuzumab + chlorambucil (category 1)
 - Ofatumumab + chlorambucil
 - Rituximab + chlorambucil
 - Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) ± rituximab
 - Obinutuzumab (category 2B)
 - Fludarabine^{c,d,e} ± rituximab (category 2B)
 - Chlorambucil (category 2B)
 - Rituximab (category 3)
 - Cladribine (category 3)^f
- Age <70 y without significant comorbidities
 - Chemoimmunotherapy
 - ◆ FCR^c (fludarabine, ^e cyclophosphamide, rituximab) (category 1)^g
 - ◆ FR^c (fludarabine, ^e rituximab)
 - ◆ PCR (pentostatin, cyclophosphamide, rituximab)
 - ◆ Bendamustine ± rituximab^g

Relapsed/Refractory therapy

[See Suggested Regimens for Relapsed/Refractory therapy for CLL without del \(11q\) or del \(17p\) \(2 of 7\)](#)

See Supportive Care for Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor lysis syndrome ([See NHODG-B](#))

See monoclonal antibody and viral reactivation ([NHODG-B](#))

[See Suggested Regimens for CLL with del \(17p\) \(3 of 7\)](#)

[See Suggested Regimens for CLL with del \(11q\) \(4 of 7\)](#)

^aSee references for regimens [CSLL-D 6 of 7](#) and [CSLL-D 7 of 7](#).

^b[See Supportive Care for Patients with CLL \(CSLL-C\)](#).

^cAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^dIn patients ≥70 y, fludarabine does not have a benefit for first-line therapy over other therapies including chlorambucil.

^eSee Discussion for further information on oral fludarabine.

^fIn rare circumstances of CNS disease, cladribine is potentially useful.

^gData from the CLL10 study confirms the superiority of FCR over BR in younger patients. For patients >65 y, the outcome was similar for both regimens with less toxicity for BR. BR may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is associated with fewer myelosuppressive toxicities.

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SUGGESTED TREATMENT REGIMENS^a

(in order of preference)

CLL without del (11q) or del (17p)

Relapsed/Refractory therapy^b

- Age ≥70 y and younger patients with significant comorbidities
 - ▶ Ibrutinib^h (category 1)
 - ▶ Idelalisib ± rituximab^{h,i}
 - ▶ Chemoimmunotherapy
 - ◊ Reduced-dose FCR^{c,e}
 - ◊ Reduced-dose PCR
 - ◊ Bendamustine ± rituximab
 - ◊ High-dose methylprednisolone (HDMP) + rituximab
 - ◊ Rituximab + chlorambucil
 - ▶ Ofatumumab
 - ▶ Obinutuzumab
 - ▶ Lenalidomide^j ± rituximab
 - ▶ Alemtuzumab^k ± rituximab
 - ▶ Dose-dense rituximab (category 2B)
- Age <70 y without significant comorbidities
 - ▶ Ibrutinib^h (category 1)
 - ▶ Idelalisib ± rituximab^{h,i}
 - ▶ Chemoimmunotherapy
 - ◊ FCR^{c,e}
 - ◊ PCR
 - ◊ Bendamustine ± rituximab
 - ◊ Fludarabine^{c,e} + alemtuzumab
 - ◊ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
 - ◊ OFAR^c (oxaliplatin, fludarabine,^e cytarabine, rituximab)
 - ▶ Ofatumumab
 - ▶ Obinutuzumab
 - ▶ Lenalidomide^j ± rituximab
 - ▶ Alemtuzumab^k ± rituximab
 - ▶ HDMP + rituximab

See Supportive Care for Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor lysis syndrome ([See NHODG-B](#))

See monoclonal antibody and viral reactivation ([NHODG-B](#))

[See Suggested Regimens for CLL with del \(17p\) \(3 of 7\)](#)

[See Suggested Regimens for CLL with del \(11q\) \(4 of 7\)](#)

^aSee references for regimens [CSLL-D 6 of 7](#) and [CSLL-D 7 of 7](#).

^b[See Supportive Care for Patients with CLL \(CSLL-C\)](#).

^cAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^eSee Discussion for further information on oral fludarabine.

^h[See Special Considerations for Use of B-Cell Receptor Inhibitors \(Ibrutinib and Idelalisib\) \(NHODG-E\)](#).

ⁱIndicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)

^jLenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

^kWhile alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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SUGGESTED TREATMENT REGIMENS^a (in order of preference)

CLL with del (17p)

First-line therapy^b

- Ibrutinib^h
- HDMP + rituximab
- FCR^{c,e}
- FR^{c,e}
- Obinutuzumab + chlorambucil
- Alemtuzumab^k ± rituximab

Relapsed/Refractory therapy^b

- Ibrutinib^h
- Idelalisib ± rituximab^{h,i}
- HDMP ± rituximab
- Lenalidomide^j ± rituximab
- Alemtuzumab^k ± rituximab
- Ofatumumab^l
- OFAR^{c,e}

[See Suggested Regimens for CLL without del \(11q\) or del \(17p\) \(1 of 7\)](#)

[See Suggested Regimens for CLL with del \(11q\) \(4 of 7\)](#)

See Supportive Care for Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor lysis syndrome ([See NHODG-B](#))

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^aSee references for regimens [CSLL-D 6 of 7](#) and [CSLL-D 7 of 7](#).

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^cAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^eSee Discussion for further information on oral fludarabine.

^h[See Special Considerations for Use of B-Cell Receptor Inhibitors \(Ibrutinib and Idelalisib\) \(NHODG-E\)](#).

ⁱIndicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)

^jLenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

^kWhile alemtuzumab is no longer commercially available in CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

^lThis is not effective in patients with lymph nodes >5 cm.

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SUGGESTED TREATMENT REGIMENS^a

(in order of preference)

CLL with del (11q)

First-line therapy^b

- Age ≥70 y and younger patients with significant comorbidities
 - ▶ Obinutuzumab + chlorambucil (category 1)
 - ▶ Ofatumumab + chlorambucil
 - ▶ Rituximab + chlorambucil
 - ▶ Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) ± rituximab^g
 - ▶ Cyclophosphamide, prednisone ± rituximab
 - ▶ Reduced-dose FCR^{c,d,e,g}
 - ▶ Chlorambucil
 - ▶ Rituximab (category 3)
- Age <70 y without significant comorbidities
 - ▶ Chemoimmunotherapy
 - ◊ FCR^{c,e,g}
 - ◊ Bendamustine ± rituximab^g
 - ◊ PCR
 - ◊ Obinutuzumab + chlorambucil

Relapsed/Refractory therapy^b

[See Suggested Regimens for Relapsed/Refractory therapy for CLL with del \(11q\) \(5 of 7\)](#)

[See Suggested Regimens for CLL without del \(11q\) or del \(17p\) \(1 of 7\)](#)

[See Suggested Regimens for CLL with del \(17p\) \(3 of 7\)](#)

^aSee references for regimens [CSLL-D 6 of 7](#) and [CSLL-D 7 of 7](#).

^b[See Supportive Care for Patients with CLL \(CSLL-C\)](#).

^cAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^dIn patients ≥70 y, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.

^eSee Discussion for further information on oral fludarabine.

^gData from the CLL10 study confirms the superiority of FCR over BR in younger patients. For patients >65 y, the outcome was similar for both regimens with less toxicity for BR. BR may be a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and is associated with fewer myelosuppressive toxicities.

See Supportive Care for Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor lysis syndrome ([See NHODG-B](#))

See monoclonal antibody and viral reactivation ([NHODG-B](#))

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SUGGESTED TREATMENT REGIMENS^a

(in order of preference)

CLL with del (11q)

Relapsed/Refractory therapy^b

- **Age ≥70 y and younger patients with significant comorbidities**
 - ▶ Ibrutinib^h (category 1)
 - ▶ Idelalisib ± rituximab^{h,i}
 - ▶ Chemoimmunotherapy
 - ◊ Reduced-dose FCR^{c,e}
 - ◊ Reduced-dose PCR
 - ◊ Bendamustine ± rituximab
 - ◊ HDMP + rituximab
 - ◊ Rituximab + chlorambucil
 - ▶ Ofatumumab
 - ▶ Obinutuzumab
 - ▶ Lenalidomide^j ± rituximab
 - ▶ Alemtuzumab^k ± rituximab
 - ▶ Dose-dense rituximab (category 2B)
- **Age <70 y without significant comorbidities**
 - ▶ Ibrutinib^h (category 1)
 - ▶ Idelalisib ± rituximab^{h,i}
 - ▶ Chemoimmunotherapy
 - ◊ FCR^{c,e}
 - ◊ PCR
 - ◊ Bendamustine ± rituximab
 - ◊ Fludarabine^{c,e} + alemtuzumab
 - ◊ OFAR^{c,e}
 - ▶ Ofatumumab
 - ▶ Obinutuzumab
 - ▶ Lenalidomide^j ± rituximab
 - ▶ Alemtuzumab^k ± rituximab
 - ▶ HDMP + rituximab

See Supportive Care for Patients with CLL ([CSLL-C](#))

Consider prophylaxis for tumor lysis syndrome ([See NHODG-B](#))

See monoclonal antibody and viral reactivation ([NHODG-B](#))

[See Suggested Regimens for CLL without del \(11q\) or del \(17p\) \(1 of 7\)](#)

[See Suggested Regimens for CLL with del \(17p\) \(3 of 7\)](#)

^aSee references for regimens [CSLL-D 6 of 7](#) and [CSLL-D 7 of 7](#).

^b[See Supportive Care for Patients with CLL \(CSLL-C\)](#).

^cAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.

^eSee Discussion for further information on oral fludarabine.

^h[See Special Considerations for Use of B-Cell Receptor Inhibitors \(Ibrutinib and Idelalisib\) \(NHODG-E\)](#).

ⁱIndicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)

^jLenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.

^kWhile alemtuzumab is no longer commercially available in CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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SUGGESTED TREATMENT REGIMENS REFERENCES

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Alemtuzumab + rituximab

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Bendamustine + rituximab

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Chlorambucil + rituximab

Hillmen P, Gribben JG, Follows GA, et al. Rituximab Plus Chlorambucil As First-Line Treatment for Chronic Lymphocytic Leukemia: Final Analysis of an Open-Label Phase II Study. *J Clin Oncol* 2014;32:1236-1241.
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Fludarabine + alemtuzumab

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[Continued on next page](#)

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Obinutuzumab

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Obinutuzumab + chlorambucil

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OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)

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PCR (pentostatin, cyclophosphamide, rituximab)

Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. *J Clin Oncol* 2006;24:1575-1581.
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RESPONSE DEFINITION AFTER TREATMENT FOR CLL^{a,b}

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

Group A criteria define the tumor load. Group B criteria define the function of the hematopoietic system (or marrow).

Complete remission (CR): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms.

Partial remission (PR): Requires 1) having two of the group A criteria if 2 or more are present. Patients with one group A criteria (excluding bone marrow) are also considered evaluable for response; 2) one group B criteria whether or not normal from baseline prior to starting therapy.

Stable disease is absence of progressive disease (PD) and failure to achieve at least a PR.

PD: appearance of any new lesions; at least one of the above criteria of group A or group B has to be met.

†Sum of the products of multiple lymph nodes (as evaluated by CT scans in clinical trials, or by physical examination in general practice).

‡These parameters are irrelevant for some response categories.

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

^bIsolated progressive lymphocytosis in the setting of reduced lymph node size or organomegaly or improvement in hemoglobin/platelets will not be considered progressive disease.

^cMRD-negative status in peripheral blood (PB) correlates with better PFS. Analysis from GCLLSG study indicates that if PB is MRD negative, residual splenomegaly has no clinical significance. Kovacs G, Boettcher S, Bahlo J, et al. *Blood* 2014;124:Abstract 23.

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Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

CLL remains the most prevalent adult leukemia in Western countries but is considered rare in regions such as East Asia. CLL/SLL comprises approximately 7% of newly diagnosed cases of NHL.³ In 2015, an estimated 14,620 people will be diagnosed with CLL in the United States, and an estimated 4,650 people will die from the disease.¹ Morphologically, the leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or prolymphocytes.⁴ CLL and SLL are different manifestations of the same disease and are managed in much the same way.⁵ CLL/SLL is characterized by progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. The major difference is that in CLL, a significant number of the abnormal lymphocytes are also found in the bone marrow and blood, while in SLL the abnormal lymphocytes are predominantly found in the lymph nodes and bone marrow.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Non-Hodgkin's Lymphomas an electronic search of the PubMed database was performed to obtain key literature in "Chronic Lymphocytic Leukemia" published between October 2013 and December 2014, using the following search terms: chronic lymphocytic leukemia, Richter syndrome, and histologic transformation. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.⁶

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

types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 67 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

Diagnosis

The diagnosis of CLL requires the presence of at least 5000 clonal B-cells/mcl ($5 \times 10^9/L$) in the peripheral blood which is established by flow cytometry quantification.⁴ The presence of fewer B-cells in the absence of palpable lymphadenopathy or other clinical features characteristic of a lymphoproliferative disorder is defined as monoclonal B-lymphocytosis (MBL). MBL is a relatively recent diagnostic category describing individuals who present with an abnormal B-cell population with immunophenotype of CLL but do not meet the diagnostic criteria for CLL.⁷ Favorable molecular lesions, mutated immunoglobulin heavy-chain variable region gene (*IGHV*) and chromosomal abnormality del(13q) or normal cytogenetics are commonly seen in individuals with MBL.⁸ The estimated rate of progression of MBL to CLL was 1.1% per year.

The CLL/SLL guideline now includes an initial stratification between CLL/SLL and MBL (absolute B-lymphocyte count of less than 5000/mm³, lymph nodes less than 1.5 cm, no thrombocytopenia or

anemia). Observation is recommended for all individuals with MBL. The diagnosis of CLL requires the presence of at least 5000 monoclonal B-lymphocytes/mcl ($5 \times 10^9/L$) in peripheral blood and the clonality of B cells should be confirmed by flow cytometry. The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with less than 5000 B-lymphocytes/mcl ($5 \times 10^9/L$) in the peripheral blood.⁴ B-cells with a CLL/SLL phenotype may be found in samples from patients with reactive lymph nodes; however, a diagnosis of SLL should only be made when effacement of the lymph node architecture is observed in biopsy samples.

Adequate immunophenotyping is essential to establish the diagnosis of CLL/SLL. Flow cytometry of peripheral blood is adequate for the diagnosis of CLL, and bone marrow biopsy is generally not required. A diagnosis of SLL should ideally be confirmed by the evaluation of lymph node biopsy. Cell surface markers for flow cytometric studies should include kappa/lambda, CD19, CD20, CD5, CD23 and CD10. If flow cytometry is used to establish a diagnosis, flow evaluation for cyclin D1 or fluorescence in situ hybridization (FISH) analysis for t(11;14) should also be included to rule out mantle cell lymphoma (MCL). Paraffin-section immunohistochemistry (IHC) on excisional or incisional lymph node biopsy materials can be performed if a diagnosis is not established by flow cytometry. Recommended IHC panel include CD3, CD5, CD10, CD20, CD23 and cyclin D1. These can be useful, particularly for diagnosing CLL/ SLL type without circulating leukemic cells.

The typical immunophenotype for CLL/SLL is CD5+, CD10-, CD19+, and CD20 dim, surface immunoglobulin dim, CD23+, CD43 +/-, and cyclin D1-. Distinguishing CLL/SLL from MCL is essential, as they are both CD5+ B-cell tumors. Though CD23 is often helpful, absence of cyclin D1 expression is critical in this differentiation of tumor types.

Stimulated cytogenetics or FISH analysis for t(11;14) can help to distinguish MCL from CLL, and should be performed if flow cytometry alone is used to evaluate immunophenotype. FISH for the detection of del(11q), del(13q), trisomy 12, del(17p), stimulated metaphase karyotype and molecular genetic analysis (by PCR or sequencing) to detect *IGHV* mutation status and *TP53* mutations can provide useful prognostic information and may guide selection of therapy.

Recent reports suggest that complex karyotype (≥ 3 unrelated chromosomal abnormalities in more than one cell on conventional karyotyping of stimulated CLL cells) is associated with an unfavorable prognosis.⁹⁻¹¹ In one report, complex karyotype was significantly associated with unmutated *IGHV* and aberrations of chromosome 17p, and it was also identified as an independent prognostic factor for shorter time-to-first-treatment.⁹ In patients with relapsed or refractory CLL treated with ibrutinib-based regimens, complex karyotype was associated with disease progression, inferior EFS and OS.^{10,11} Cytogenetic abnormalities can evolve over time; therefore, re-evaluation of FISH and karyotype is necessary to direct treatment options in patients with indications for treatment.

Conventional metaphase cytogenetics is difficult in CLL as a result of the very low *in vitro* proliferative activity of the leukemic cells. Therefore, interphase cytogenetic analysis with FISH is the standard method to detect chromosomal abnormalities that may have prognostic significance. However, FISH can only detect abnormalities specific to the probes utilized. Cytokine or CpG oligonucleotide stimulation was utilized to enhance metaphase analysis.¹² Recent studies demonstrated that stimulation with CpG oligonucleotide and interleukin-2 is more effective than that with 12-O-tetradecanoyl-phorbol-13-acetate (TPA) for the detection of chromosomal abnormalities in CLL.^{13,14} A prospective study conducted by CLL

Research Consortium confirmed that abnormal clones in CLL are more readily detected with CpG oligonucleotide stimulation than with traditional B-cell mitogens; moreover, the clonal abnormalities revealed by CpG stimulated metaphase cytogenetics are consistent with that detected by interphase FISH and are reproducible among different cytogenetic laboratories.¹⁵ However, the use of CpG stimulation for CLL cytogenetics is not yet universally available.

Prognostic Factors

During the past decade, numerous factors were identified and evaluated in patients with CLL, which may provide useful prognostic information beyond clinical staging (see Discussion section below for 'Staging'). These factors include serum markers such as thymidine kinase and beta-2 microglobulin, genetic markers including *IGHV* mutational status and cytogenetic abnormalities detected by FISH (e.g., del(13q), del(11q), del(17p)), CD38 expression, CD49d and ZAP-70 expression/methylation).¹⁶⁻²⁸

IGHV mutational status is an important predictor of survival outcomes in CLL; unmutated *IGHV* ($\geq 98\%$ homology with germline gene sequence) is associated with poor prognosis and significantly decreased survival compared with cases with mutated *IGHV*, irrespective of the stage of the disease.^{17,22} In addition, *VH3-21* gene usage was associated with poor outcomes regardless of the mutation status (as defined by percent homology with germline sequence).²⁹ Unmutated *IGHV* or the use of *VH3-21* was shown to be independent predictors of shorter treatment-free interval and/or survival outcomes, even when high-risk genomic abnormalities (see Discussion below on cytogenetic abnormalities detected by FISH) were included in the multivariable regression models.³⁰⁻³³

Expression of CD38 ($\geq 7\%$ of B lymphocytes)^{17,18,24,31,32,34} and/or ZAP-70 ($\geq 20\%$ of B lymphocytes)^{16,25-27,35} were also associated with shorter progression-free survival (PFS) and overall survival (OS) outcomes. Among the flow cytometry based prognostic assays (CD38, ZAP-70, and CD49d), CD49d appears to be the strongest prognostic parameter and is the only one that is independent of FISH and *IGHV*.²⁸ Both CD38 and ZAP-70 positivity correlate with unmutated *IGHV*, and were suggested as potential surrogate markers for *IGHV* mutational status.^{16,17,27} However, discordant results between CD38 positivity and *IGHV* mutational status were observed in up to 28% of patients in one study; moreover, CD38 expression levels may vary over the course of the disease.²³ Similarly, discordant results between ZAP-70 positivity and *IGHV* mutational status were reported in 20-25% of cases.^{26,32} In addition, it was suggested that ZAP-70 positivity may be a stronger predictor of outcomes (e.g., time to first treatment) than *IGHV* mutational status or CD38 levels.^{26,35,36} ZAP-70 methylation analysis (which is closely associated with ZAP-70 expression and *IGHV* mutational status) was also reported to be a useful prognostic test for patients with CLL.³⁷⁻³⁹ CD38 and/or zeta-associated protein 70 (ZAP-70) expressions can be determined using IHC, flow cytometry or methylation. However, standardization and reproducibility of ZAP-70 expression across laboratories remains a challenge. Evaluation of ZAP-70 protein expression is not recommended outside the context of clinical trials. Therefore, in clinical practice, *IGHV* mutation testing is recommended based on reproducibility and ready availability.

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, including in patients treated with first-line chemoimmunotherapy regimens.⁴⁰⁻⁴² One of the advantages of beta-2 microglobulin is that it is readily measured by standard

laboratory evaluation of blood samples. However, it is influenced in a CLL disease independent manner by renal dysfunction. Wierda et al developed a prognostic nomogram using clinical and laboratory parameters that are available in the routine clinical practice setting (age, beta-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph nodes); the nomogram was developed to estimate the median survival time, as well as the probability of 5-year and 10-year survival. In addition, based on the sum of points assigned to the six parameters used for the nomogram, a more simplified prognostic index was developed to help stratify untreated patients with CLL into three different risk groups (low, intermediate and high).⁴³ The estimated median survival was not reached for the low-risk group. The median survival times for intermediate- and high-risk groups were 10 and 5 years, respectively. The 5-year survival rates were 97% for low-risk, 80% for intermediate-risk, and 55% for high-risk groups; the 10-year survival rates were 80%, 52%, and 26%, respectively.⁴³ It should be noted that sufficient data were not available for recently identified prognostic factors (e.g., *IGHV* mutational status, ZAP-70, cytogenetic abnormalities detected by FISH) to be incorporated into this version of the prognostic model (see Discussion section that follows for a recent prognostic nomogram that includes newer biological factors in addition to clinical and laboratory parameters, for estimating time to first treatment). Nevertheless, several studies independently confirmed the utility of this prognostic index in estimating both survival probability and time to first treatment in previously untreated patients with CLL, including in patients with early-stage (Rai stage 0) disease.^{44,45}

Cytogenetic abnormalities that can be detected by FISH are present in over 80% of patients with previously untreated CLL. FISH is categorized according to the highest-risk abnormality present,

according to a hierarchical categorization. The most common abnormality is del(13q) (55%) as a sole finding, followed by del(11q) (18%), trisomy 12 (16%), del(17p) (7%), and del(6q) (7%).¹⁹ 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).^{19,46} Among patients with del(11q), those with a complete loss of *ATM* function might have impaired response to irradiation or cytotoxic drugs, resulting in poor clinical outcome.⁴⁷ Recent studies showed that previously untreated patients with del(11q) respond well to combination therapy with fludarabine and cyclophosphamide (FC), suggesting that the addition of an alkylating agent to fludarabine may help to overcome the adverse prognostic significance of del(11q) in patients with CLL.^{32,48} Del(17p), which reflects the loss of the *TP53* gene and is frequently associated with mutations in the remaining *TP53* allele, is associated with worst outcomes, with short treatment-free interval, short median survival (32 months), and poor response to chemotherapy.¹⁹ The phase III randomized CLL8 study of the German CLL Study Group (first-line FC vs. rituximab combined with FC [FCR]) showed that both del(17p) and unmutated *IGHV* were significant independent predictors of poor survival outcomes, irrespective of the treatment arm.⁴⁹ Although FCR was associated with significantly improved PFS among patients with del(17p), the 3-year PFS rate was only 18% in this subgroup. In addition, OS outcomes in patients with del(17p) were similar between FCR and FC arms (3-year OS 38% vs. 37%, respectively).⁴⁹ The prognostic importance of del(17p) may be dependent on the proportion of malignant cells with this abnormality. In the UK CLL4 trial (comparing first-line therapy with chlorambucil vs. fludarabine vs. FC), similar outcomes were observed between patient subgroups with 5% to 10% of cells with *TP53* deletion (i.e., del(17p13.1)) and the

subgroup without *TP53* deletion (deletion in <5% of cells); patients with 10% to 20% *TP53* deletion had outcomes similar to patients with more than 20% *TP53* deletion.^{32,50} Patients with 10% or more cells with *TP53* deletion had a poor outcome with 29% response rate (6% complete or nodular partial response) and a median survival of <6 months.³² The finding that del(17p) is more frequently observed in treated patients than in untreated patients suggests that treatment-driven clonal selection may occur during therapy. Indeed, acquisition and/or expansion of CLL clones with del(17p) were observed during the course of treatment.⁵¹

A prognostic nomogram for estimating time to first treatment was developed based on a multivariable model that included both traditional clinical and laboratory parameters as well as newer prognostic factors (such as FISH cytogenetics, *IGHV* mutational status, and ZAP-70 expression levels).⁵² The following factors were identified as independent predictors of shorter time to first treatment, and were included in a weighted model to estimate the probability of treatment (at 2- and 4-years) and time to first treatment: increased size of cervical lymph nodes, 3 involved nodal sites, del(17p) or del(11q), unmutated *IGHV* status, and elevated serum LDH levels.⁵² This nomogram may help to identify newly diagnosed patients at high risk for disease progression who may require earlier intervention. More recently, the German CLL Study Group developed a comprehensive prognostic index to stratify patients into 4 risk groups based on OS. In this model, sex, age, ECOG status, del(17p), del(11q), *IGHV* mutation status, serum beta-2 microglobulin, and serum thymidine kinase were identified as independent predictors of OS in patients newly diagnosed patients.⁵³

Abnormalities of *TP53* can be observed in the absence of del(17p).^{54,55} Studies with fludarabine-based regimens identified *TP53* mutations as

an independent predictor of decreased survival and resistance to chemotherapy.⁵⁴⁻⁵⁷ Resistance to chemotherapy was attributed to the presence of mutation in the remaining *TP53* allele.⁵⁵ Thus, the presence of *TP53* mutation predicts for poor survival outcomes independent of 17p chromosome status.⁵⁴ In an analysis from the CLL8 study, mutation in *TP53* was associated with significantly decreased PFS and OS outcomes regardless of treatment with FCR or FC.⁵⁵

The impact of these prognostic factors on the clinical outcome of patients was examined in large prospective randomized studies. In the long-term follow up from the CALGB 9712 study (first-line therapy with concurrent vs. sequential fludarabine and rituximab), unmutated *IGHV* was a significant independent predictor for shorter PFS and OS, while poor-risk cytogenetic abnormalities (i.e., del(17p) or del(11q)) remained an independent predictor for shorter survival.⁵⁸ In the UK CLL4 trial, *TP53* loss was found to be the strongest predictor of poor outcomes.^{32,56} Among the subgroup of patients without *TP53* loss, unmutated *IGHV* (or *VH3-21* usage) and elevated beta-2 microglobulin (>4 mg/L) were significant independent predictors for both PFS and OS outcomes.³² In addition, del(11q) and treatment allocation were independent predictors for PFS and age was an independent predictor for OS. In the German CLL8 trial (first-line FC vs. FCR), mutated *TP53*, del(17p), unmutated *IGHV*, and treatment arm were significant independent prognostic factors for both PFS and OS outcomes.⁵⁵

During the last few years, recurrent mutations in *NOTCH1*, *SF3B1* and *BIRC3* genes with prognostic implications in CLL were identified.⁵⁹⁻⁶³ In most of the published series, *NOTCH1*, *SF3B1* and *BIRC3* mutations were observed in approximately 4% to 15% of patients with newly diagnosed CLL and the incidences are much higher (15% to 25%) in patients with CLL refractory to fludarabine.^{59,61,63} Messina et al recently

reported that recurrent mutations in one or more genes including *TP53* (27.5%), *NOTCH1* (24.1%), *SF3B1* (18.9%), and *BIRC3* (15.5%) are present in more than 70% of CLL refractory to fludarabine.⁶⁴ Rossi et al proposed an integrated prognostic model including *NOTCH1*, *SF3B1*, and *BIRC3* mutations along with the cytogenetic abnormalities identified by FISH to classify patients into 4 distinct prognostic subgroups: high-risk (*TP53* and/or *BIRC3* abnormalities); intermediate-risk (*NOTCH1* and/or *SF3B1* mutations and/or del11q); low-risk (trisomy 12 and wild-type for all genetic lesions) and very low-risk (del13q only).⁶⁵ The 10-year survival rates for the 4 subgroups were 29%, 37%, 57% and 69% respectively.

Data from prospective clinical trials confirmed that *NOTCH1* and *SF3B1* mutations are predictors of shorter survival in patients with newly diagnosed as well as relapsed or refractory CLL.^{55,66,67} In the UK CLL4 trial showed that both *NOTCH1* and *SF3B1* mutations were associated with shorter OS, and both retained independent prognostic significance for survival outcomes based on multivariable analysis.⁶⁶ Contrastingly, in the German CLL2H study, *NOTCH1* mutations were associated with longer PFS compared with wild-type cases, and *SF3B1* mutations had no impact on PFS or OS. In a multivariable analysis, *NOTCH1* mutation was found to be an independent predictor of favorable PFS in patients with fludarabine-refractory CLL.⁶⁷ In the CLL8 trial, *TP53* and *SF3B1* mutations were the strongest prognostic markers in patients receiving current-standard first-line therapy whereas *NOTCH1* mutation was identified as a predictive marker for decreased benefit from the addition of rituximab to FC.⁵⁵ The impact of these mutations relative to treatment with newer targeted therapies is uncertain.

NOTCH1 mutation was also independently associated with Richter's transformation.^{68,69} In a recent study based on data from a large

multicenter series of newly diagnosed patients with CLL, the cumulative probability of developing Richter's transformation was significantly higher for patients with *NOTCH1* mutations at diagnosis compared to those without the mutation (45% vs. 5% at 15 years; $P < 0.001$).⁶⁸

Collectively, the above studies suggest that the prognostic significance of these mutations may vary depending on the patient population, treatment regimens, and clinical outcomes being evaluated. Although these prognostic factors may provide useful prognostic information, treatment initiation or selection of treatment options should not be driven by these factors. Moreover, in the general clinical practice setting, prognostic factors should not determine treatment choices, with the exception of del(17p) or del(11q).

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.^{41,43} Though classically, the pattern of bone marrow involvement (diffuse vs. nodular) had prognostic significance, this is no longer a factor when one uses more reliable prognostic markers such as *IGHV* mutational status and cytogenetic abnormalities determined by FISH, all of which can be obtained by analysis of circulating lymphocytes. Thus, bone marrow biopsy is no longer considered a required part of the diagnostic evaluation of patients with suspected CLL, though it remains useful to evaluate the etiology of cytopenias.

Computed tomography (CT) scans may be useful to follow and monitor disease progression in patients with new symptoms when peripheral adenopathy is not present. For asymptomatic patients,

serial CT scans are not recommended. For anemic patients, reticulocyte counts and a direct Coombs' test should be performed to evaluate for the possibility of hemolysis and pure red aplasia. PET scan is generally not useful in CLL but can assist in directing nodal biopsy if Richter's transformation is suspected.^{70,71} Bone marrow biopsy ± aspirate could be useful in certain circumstances prior to initiation of treatment.

Staging

Two staging systems, the Rai and Binet systems are currently used worldwide in the evaluation of patients with CLL both in the routine practice and clinical trial settings.^{72,73} Both staging systems rely solely on physical examination (presence of lymph node involvement, enlarged spleen and/or liver) and blood parameters (presence of anemia or thrombocytopenia) to assess the degree of tumor burden. The modified Rai classification stratifies patients into 3 risk groups. Survival of patients with low-risk disease (Rai stage 0; median survival 150 months) is essentially the same as the survival rate of age-matched controls. Patients with intermediate-risk disease (Rai stage I-II; median survival 71-101 months) have shorter survival, particularly when other adverse factors coexist, such as a lymphocyte doubling time of less than one year. Patients with high-risk features (Rai stage III-IV; median survival 19 months) have poor prognosis.⁷² The Binet staging system is based on the number of involved areas and the level of hemoglobin and platelets and similar to the Rai staging system, provides meaningful correlation with clinical outcome.⁷³ The nearly universal involvement of the bone marrow and peripheral blood in CLL/SLL limits the utility of the Ann Arbor staging system.

Response Criteria

The National Cancer Institute-sponsored Working Group (NCI-WG) on CLL published guidelines for the diagnosis and management of CLL in 1988 and 1996, primarily to facilitate consistency in the design and conduct of clinical trials. Most clinical trials of CLL reporting response outcomes have, until very recently, utilized the response criteria set forth in the 1996 NCI-WG guidelines.⁷⁴ In 2008, the NCI-WG guidelines were revised to reflect recent advances in our understanding of newer prognostic markers, diagnostic parameters, and treatments.⁴ In particular, the 2008 guidelines provide further recommendations on the evaluations and response assessments appropriate for the general clinical practice setting versus for clinical trials.⁴

In the clinical practice setting, response assessment involves both physical examination and evaluation of blood parameters. For a complete response (CR), all of the following criteria must be met (at least 2 months after treatment completion): peripheral blood lymphocyte counts $<4 \times 10^9/L$; absence of lymphadenopathy (i.e., palpable nodes must be ≤ 1.5 cm in diameter); absence of splenomegaly or hepatomegaly; absence of constitutional symptoms (i.e., weight loss, significant fatigue, fevers, night sweats); and normalization of blood counts without growth factor support (i.e., neutrophils $>1.5 \times 10^9/L$, platelets $>100 \times 10^9/L$, hemoglobin >11 g/dL).⁴ For a partial response (PR), at least 2 of the following criteria must be met for at least 2 months duration: at least 50% reductions from baseline in peripheral blood lymphocyte counts, lymphadenopathy (based on sum of the products of multiple affected nodes), hepatomegaly, and/or splenomegaly; in addition, at least 1 of the blood counts should be normalized or increase by $\geq 50\%$ from baseline, for at least 2 months duration. Progressive disease

comprises any of the following: at least 50% increase from baseline in lymphocyte counts, lymphadenopathy, hepatomegaly, or splenomegaly, appearance of any new lesions, or occurrence of cytopenias attributable to disease (i.e., $\geq 50\%$ decrease from baseline in platelet count, >2 g/dL decrease from baseline in hemoglobin levels).⁴ Patients who do not have progressive disease but do not meet the criteria for a CR or PR are considered to have stable disease. Relapse is defined as evidence of disease progression after a period of 6 months or more following an initial CR or PR. Refractory disease is defined as failure to achieve a response or having disease progression within 6 months of the last treatment.⁴

CT scans are desirable in clinical trials for evaluations of adenopathy and organ involvement and select patients outside of trials. In addition, a bone marrow evaluation should be conducted to confirm a CR ($<30\%$ lymphocytes, normocellular morphology, absence of lymphoid nodules) if all other criteria for clinical CR (as defined above) are met. Patients who fulfill the criteria for a CR (including evaluation of the bone marrow) but present with persistent cytopenias due to treatment-related toxicities, should be considered as having achieved a CR with incomplete marrow recovery (CRi).⁴

These response criteria were recently revised to more precisely predict the outcome for patients with CLL treated with immunomodulating agents and small molecule kinase inhibitors (ibrutinib and idelalisib).⁷⁵ Treatment with immunomodulating agents such as lenalidomide results in a tumor flare reaction (TFR) characterized by painful enlargement of lymph nodes and lymphocytosis, rash, and bone pain; TFR was correlated with clinical response in patients with CLL treated with lenalidomide.⁷⁶ Similarly the use of small molecule inhibitors of BCR-signalling pathway (ibrutinib and idelalisib) was known to result in an initial transient increase in lymphocytosis resulting from the

redistribution or release of leukemic cells from the lymph node compartment to the peripheral blood.^{77,78} In the majority of patients treated with ibrutinib, lymphocytosis resolves within 8 months, but in a subgroup of patients lymphocytosis lasts for more than 12 months. Prolonged lymphocytosis following ibrutinib treatment was reported to represent the persistence of a quiescent clone and does not predict a subgroup of patients likely to relapse early.⁷⁹ Considering these findings, for patients receiving idelalisib and ibrutinib, the revised response criteria recently proposed by Cheson et al allow for a new response category, "PR with lymphocytosis," to include those with a clinical response (reduction in lymph nodes and splenomegaly) with persistent lymphocytosis (in the absence of other indicators of progressive disease).⁷⁵

Minimal residual disease (MRD) negativity determined in the peripheral blood after the end of treatment is emerging as an important predictor of treatment efficacy. In the combined analysis of two phase III GCLLSG studies, among patients who achieved CR, there was a statistically significant difference in PFS between MRD-negative and MRD-positive patients (69.2 months vs. 40.4 months; $P = .001$).⁸⁰ The persistence of post treatment splenomegaly as a sole abnormality in MRD-negative patients had no negative influence on PFS. These results support the use of MRD for response evaluation.

Treatment Options

During the last several decades, therapeutic options for CLL have evolved from the use of alkylating agent monotherapy to purine analog-based combination regimens. The advent of monoclonal antibodies that target cell surface antigens (e.g., CD20, CD52) and immunomodulating agents (e.g., lenalidomide) led to the development of new and effective combination chemoimmunotherapy regimens. A large number of

ongoing clinical trials are evaluating novel combination regimens including drugs with different mechanism action.

First-line Therapy

In an early clinical trial, the efficacy of chlorambucil plus prednisone was found to be comparable to that of CVP (cyclophosphamide, vincristine and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimens in previously untreated patients with advanced CLL.⁸¹

The randomized CALGB 9011 study evaluated first-line treatment with fludarabine, chlorambucil or the combination (n=509).⁸² The combination arm was stopped early due to excessive toxicity; response rates were similar to fludarabine alone. Fludarabine, compared with chlorambucil, resulted in significantly improved CR rate (20% vs. 4%), PR rate (43% vs. 33%), median response duration (25 months vs. 14 months) and median PFS (20 months vs. 14 months). The study found no significant difference in median OS between the 2 arms (66 months vs. 56 months for chlorambucil), although it should be noted that this result included data from patients who crossed over from one treatment arm to the other.⁸² The long-term survival analysis suggests a potential survival advantage for fludarabine compared to chlorambucil, which is evident after 5 to 6 years of treatment. After a median follow-up of slightly more than 5 years, OS rates at 6 and 8 years were 43% and 31%, respectively for fludarabine and 38% and 19% respectively for chlorambucil.⁸³

An European randomized study compared fludarabine with two alkylating agent-based combination regimens, CAP (cyclophosphamide, doxorubicin and prednisone) and CHOP as first-line treatment in patients with advanced CLL (n=938).⁸⁴ Fludarabine and CHOP produced similar overall remission rates

(ORR; 71%) compared to CAP (58%); CR rates were significantly different between fludarabine (40%), CHOP (30%), and CAP (15%), although median survival times were similar (69, 67, and 70 months, respectively). Fludarabine was found to have a more preferable tolerability profile than CHOP.

In a phase III randomized trial (CLL5 study) conducted by the German CLL Study Group, 193 older patients with previously untreated CLL (age >65 years; median age 70 years) were randomized to either fludarabine or chlorambucil (n=193).⁸⁵ Fludarabine, compared with chlorambucil, resulted in significantly improved ORR (72% vs. 51%), CR rates (7% vs. 0%), and median time to treatment failure (18 months vs. 11 months). However, no advantage with fludarabine was observed for PFS (median 19 months vs. 18 months) or OS (median 46 months vs. 64 months) outcomes.⁸⁵ Thus, chlorambucil remains a valid first-line treatment option for older patients or in patients with comorbidities for whom more intensive regimens are not appropriate.

The combination of fludarabine and cyclophosphamide (FC) was compared with fludarabine monotherapy in relatively young patients (median age 58 to 64 years) with previously untreated CLL in several large randomized phase III trials.^{50,86,87} Treatment with FC resulted in significantly improved ORR (74-94%), CR rates (23-38%) and PFS (median 32-48 months) compared with fludarabine monotherapy.^{50,86,87} No significant differences in OS outcomes were observed between treatment arms in these studies.

Lenalidomide, an immunomodulating agent was evaluated as first-line therapy in several studies.⁸⁸⁻⁹¹ In a phase II study in patients with previously untreated CLL (n=25), lenalidomide (initial dose 2.5 mg daily, with dose escalation up to 10 mg daily; given 21 days of 28-day cycle) resulted in an ORR of 56% (all partial responses, no CRs) with

a median duration of response of approximately 17 months at a median follow up of 21 months.⁸⁸ Tumor flare reactions occurred in 88% of patients but were all grade 1 or 2 events. The most common grade 3 or 4 toxicities included neutropenia (72%; grade 4 in 32%), thrombocytopenia (28%; grade 4 in 16%) and anemia (20%; grade 4 in 4%). Grade 3 or 4 infections or febrile events were reported in 36% (grade 4 febrile neutropenia in 8%). After an extended median follow up of 53.2 months, the ORR was 72% (20% CR).⁸⁹ The 3-year PFS and OS rates were 65% and 85%, respectively. Recurrent myelosuppression was common during long-term treatment.

In another phase II study, lenalidomide (initial dose of 5 mg daily, with dose escalation up to 25 mg; given daily for 28 days of 28-day cycle) was evaluated in previously untreated patients 65 years or older (n=60).⁹⁰ In this study, the ORR was 65% with CR in 10% and incomplete CR (CRi; CR with residual cytopenias) in an additional 5% of patients. The median time to achieving a CR/CRi was 18 months (range, 9–27 months). After a median follow up of 31 months, the PFS and OS rates were 60% and 88%, respectively.⁹⁰ Interestingly, the subgroup of patients with unmutated *IGHV* (n=33) showed an ORR of 76% with a CR/CRi rate of 24%. Among the subgroup of patients with del(11q), the ORR was 64% with a CR/CRi rate of 21%. None of the patients with del(17p) had a response, and the median PFS in this poor-risk subgroup was only 6 months. The most common grade 3 or 4 toxicities included neutropenia (83%; grade 4 in 67%) and thrombocytopenia (47%; grade 4 in 8%). Grade 3 or 4 infections or febrile events were reported in 13% of patients. Tumor flare reactions (all grade 1 or 2 events) occurred in 52% of patients.⁹⁰ In an updated analysis from this study, with a median follow up of 48 months, the median time to treatment failure was not reached and the OS rate was 82%.⁹¹ The updated analysis reported that 35 patients (58%) achieved

responses lasting 36 months or longer, and 25 of these patients were still on therapy; no deaths occurred among the long-term responders.⁹¹ Lenalidomide appeared to show promising activity in the first-line setting in CLL, particularly for older patients and for those with del(11q). A follow up randomized phase III study (ORIGIN trial) evaluating monotherapy with lenalidomide vs. chlorambucil as initial therapy for CLL in elderly patients older than 65 years demonstrated early mortality with lenalidomide.⁹² This study was recently halted by the FDA due to concerns for increased risk of death in the lenalidomide arm vs. chlorambucil arm. Evaluation of lenalidomide as initial therapy for elderly patients with CLL should occur only in the context of a clinical trial based upon these results.

Bendamustine is an alkylating agent with a purine-like benzimidazole ring component, with a low cross-resistance with other alkylating agents due to its unique cytotoxic properties. In a pivotal phase III randomized study that compared the safety and efficacy of bendamustine with chlorambucil in patients with previously untreated CLL (n = 319), treatment with bendamustine, compared with chlorambucil, resulted in significantly higher ORR (68% vs. 31%; $P<0.0001$) and CR rate (31% vs. 2%; $P<0.0001$).^{93,94} The higher response rates and PFS benefit with bendamustine was retained in the subgroup of patients 65 years or older. The incidences of grade 3 or 4 hematologic toxicities, infections, and gastrointestinal events were higher with bendamustine than with chlorambucil.⁹³ No differences in OS outcomes were observed between the two groups. After a median follow-up of 54 months, the median PFS was significantly longer with bendamustine (21 months vs. 9 months; $P<0.0001$).⁹⁴ The efficacy of bendamustine compared to first-line therapies other than chlorambucil has not yet been established.

The introduction of the CD20 monoclonal antibody rituximab led to important advances in the treatment of CLL, particularly in the context of chemoimmunotherapy. In the first-line treatment setting, rituximab monotherapy resulted in modest activity with 51% ORR and 4% CR (based on the standard 4 weekly infusions; N=44); the median PFS was approximately 19 months.⁹⁵ Given the favorable tolerability profile, rituximab monotherapy may be an appropriate treatment option for a small fraction of elderly patients (≥ 70 years) who present with substantial comorbidities or decreased performance status.

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

Rituximab in combination with chlorambucil has been evaluated in phase II studies with reasonable ORR and CR rates of 82.5% - 84% and 10% - 16.5%, respectively.^{97,98} However, in the CLL11 trial that compared chlorambucil in either combination with rituximab or obinutuzumab, there was a clinically meaningful improvement in PFS with a trend towards improved OS in patients treated with obinutuzumab + chlorambucil versus rituximab + chlorambucil.⁹⁹ Thus, first-line treatment with rituximab and chlorambucil should be reserved for patients who cannot tolerate obinutuzumab.

The CALGB 9712 study evaluated the efficacy of fludarabine with concurrent or sequential administration of rituximab in untreated patients with CLL.^{58,100} The concurrent regimen was associated with a higher ORR (90% vs. 77% for the sequential regimen) and CR rate (47% vs. 28%) at the expense of higher incidence of grade 3 or 4 toxicity (primarily comprising neutropenia and infusion-related events).¹⁰⁰ The long-term follow up from the CALGB 9712 study (median follow-up time 117 months) reported a median PFS of 42 months (5-year PFS rate 27%) and median OS of 85 months.⁵⁸ Comparison of the outcomes of patients treated with fludarabine alone in the CALGB 9011 trial with the pooled results from the CALGB 9712 study suggested that the addition of rituximab to fludarabine prolongs PFS and OS.¹⁰¹

The combination of fludarabine, cyclophosphamide and rituximab (FCR) evaluated at MD Anderson Cancer Center as initial therapy (n=300) produced high ORR and CR rate.^{40,102} At a median follow up of 6 years, the ORR was 95% (72% CR); the median time to progression was 80 months and the 6-year OS rate was 77%.⁴⁰ A large international randomized Phase III clinical trial (CLL8 study) showed that the addition of rituximab to fludarabine-based chemotherapy improved the outcome of patients with CLL with regard to response rates, PFS and OS compared to those receiving fludarabine-based chemotherapy alone.⁴⁹ In this trial, physically fit patients with previously untreated CLL (median age 61 years; n=817) were randomized to receive up to 6 courses of either FCR or FC regimen. The FCR regimen resulted in higher ORR (95% vs. 88%) and CR rate (44% vs. 22%) compared with FC. The median PFS was 52 months with FCR and 33 months with FC ($P < .001$). At 3 years after randomization, the FCR regimen significantly improved both PFS rate (65% vs. 45%; $P < .0001$) and OS rate (87% vs. 83%; $P < 0.0001$).

compared with FC alone. The FCR regimen was associated with significantly higher incidence of grade 3 or 4 neutropenia compared with FC (34% vs. 21%; $P < .0001$); the incidence of severe infections and treatment-related deaths were similar between treatment arms. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously untreated CD20-positive CLL.

Pentostatin is another purine analog that was evaluated as part of chemoimmunotherapy regimens in the first-line treatment of CLL. In a phase II trial initiated by two member institutes of the CLL Research Consortium, pentostatin, cyclophosphamide and rituximab (PCR) demonstrated significant clinical activity despite the large proportion of patients with poor-risk prognostic factors (e.g., high-risk Rai stage in 53%; unmutated *IGHV* in 71%; FISH abnormalities in 52%) in this trial ($n=64$).¹⁰³ Responses were observed in 91% of patients (41% CR); median response duration (among responders) was 34 months. The median PFS for all patients on the trial was approximately 33 months.¹⁰³ The toxicities were manageable, and appeared less myelotoxic relative to FCR regimens. A subsequent study investigated the possibility of reducing the toxicity of the PCR regimen by omitting cyclophosphamide (and using a higher dose of pentostatin) in previously untreated patients ($n=33$).¹⁰⁴ The combination of higher dose pentostatin with rituximab (PR) resulted in 76% ORR, with CR in 27% of patients.¹⁰⁴ Relative to historical outcomes with the PCR regimen, however, the response rates with PR were lower and the median treatment-free survival was also decreased (16 months vs. 30 months for PCR), suggesting that cyclophosphamide is an important component in the activity of PCR regimens. A community-based multicenter phase III randomized trial ($n=184$) using higher dose pentostatin was conducted by US Oncology Research to compare the

safety of PCR with FCR regimens in previously untreated (80% of patients) or minimally pretreated patients.¹⁰⁵ The ORR with PCR and FCR were similar (49% vs. 59%), with a lower CR rate in the PCR group (7% vs. 14%; $P=0.04$). The incidence of grade 3 or 4 infectious events and neutropenia were similar between treatment arms, with increased incidence of leukopenia and thrombocytopenia in the FCR group.¹⁰⁵ Overall, the PCR regimen did not appear to provide an advantage over FCR in terms of toxicity profile or clinical activity.

Chemoimmunotherapy with bendamustine and rituximab (BR) was also evaluated in patients with previously untreated CLL.¹⁰⁶⁻¹⁰⁸ In a multicenter phase II trial (CLL2M study) from the German CLL Study Group, BR showed high response rates (ORR 88%; CR 23%) in previously untreated patients ($n=117$; 26% of patients were older than 70 years), with similar response and survival outcomes among the subgroup of elderly patients (age >70 years).¹⁰⁶ The median duration of response was 31 months. After a median observation time of 27 months, the median PFS for all patients was 34 months, and OS rate was 90.5%. However, the BR regimen appeared to have limited activity in patients with *del(17p)*. In the small subgroup of patients with *del(17p)* ($n=8$), the ORR (all partial remissions) was 37.5% and median PFS was only 8 months.¹⁰⁶ The most common grade 3 or 4 toxicities included thrombocytopenia (22%), neutropenia (20%), anemia (20%), allergic/infusion reactions (9%), and infections (8%).¹⁰⁶

An ongoing phase III randomized trial is comparing BR with rituximab and chlorambucil (R-chlorambucil) as first-line or second-line therapy in patients with CLL who are not candidates for fludarabine-based chemoimmunotherapy due to older age or the presence of comorbid conditions. In the interim analysis of this trial, (126 evaluable patients; 58 patients treated with BR; 68 patients treated with R-chlorambucil; median age 74 years, range 44–91), the ORR was 88% in the BR group

(CR in 30%) and 80% (CR in 13%) in the R-chlorambucil group, among the patients who received first-line therapy.¹⁰⁷ A higher proportion of patients in the BR group had poor-risk features including del(17p) or del(11q) (12% vs. 4%) and unmutated *IGHV* (53% vs. 38%) compared with the R-chlorambucil group. The toxicity profile was similar between treatment groups, with the most common grade 3 or 4 toxicity being neutropenia (BR, 32%; R-chlorambucil, 34%).

The phase III randomized study (CLL10 study) compared BR with FCR as first-line therapy for fit patients ($n = 567$; CIRS score ≤ 6 , creatinine clearance > 70 ml/min) without del(17p).¹⁰⁸ The median age was 61.6 years for all patients, but significantly higher proportion of patients were ≥ 70 years in the BR arm (22% vs 14%). The median follow-up was 35.9 months. Among the 547 patients evaluable for response, the ORR was 97.8% ($P = 1.0$) in both treatment groups, with no difference in OS (90.6% for FCR vs 92.2% for BR; $P = .910$). However, FCR resulted in higher CR rate (40.7% vs. 31.5%; $P = .026$), more MRD negativity (58.2% vs. 26.3% at 12 months; $P < .001$; 53.8% vs. 24.6% at 18 months; $P = .006$) and longer median PFS (53.7 months vs. 43.2 months; $P = .001$) compared to BR. The benefit of FCR was the most in physically fit patients younger than 65 years. The incidence of severe infections were significantly more frequent in the FCR arm (39.8% vs 25.4%, $P = .001$), especially in older patients (48.4% vs 26.8%; $p = 0.001$). The results of the study confirm that FCR remains the standard first-line therapy for untreated CLL in fit patients. BR is an alternative treatment option for elderly fit patients or patients with previous infections.

Lenalidomide in combination with rituximab was also evaluated in previously untreated patients with CLL. In a multicenter phase II study of the CLL Research Consortium, previously untreated patients with CLL ($n = 69$) were treated with lenalidomide (initial dose 2.5 mg daily,

with dose escalation up to 10 mg daily; given 21 days of a 28-day cycle) combined with rituximab (dose escalated to 375 mg/m² cycle 1; 375 mg/m² weekly for 4 weeks in cycle 2, then on day 1 for cycles 3–7).¹⁰⁹ Patients in this trial were stratified by age group (age < 65 years, $n = 40$; age ≥ 65 years, $n = 29$). Only 59% of the older patient group completed the planned 7 cycles of therapy compared with 88% of patients younger than 65 years. Tumor flare reaction (predominantly grade I-II) occurred in 83% of patients aged < 65 years and in 66% of patients aged ≥ 65 years. The most common grade 3 or 4 toxicity was neutropenia, which was reported in 76% of patients. Among evaluable patients ($n = 65$), the ORR was 95% (20% CR and 20% nodular PR) in patients younger than 65 years ($n = 38$) and the ORR in patients 65 years or older ($n = 27$) was 79% (10% CR). After a median follow-up of more than 20 months, the median PFS was 19 months and 20 months, respectively, for the younger and older cohort; median OS was not reached in either arm.¹⁰⁹

Alemtuzumab, a humanized CD52 monoclonal antibody, was initially approved for fludarabine-refractory CLL and has since shown activity as a first-line treatment for patients with CLL, both as a monotherapy and in combination regimens.¹¹⁰⁻¹¹² In an international, multicenter randomized phase III study (CAM307), previously untreated patients with CLL ($n = 297$) were randomized to receive alemtuzumab or chlorambucil.¹¹¹ Alemtuzumab resulted in a significantly higher ORR (83% vs. 55%; $P < .0001$) and CR rate (24% vs. 2%; $P < .0001$) than chlorambucil; in addition, a modest but statistically significant benefit in PFS was observed with alemtuzumab compared with chlorambucil (median 15 months vs. 12 months; $P = .0001$). In the small subgroup of 21 patients with del(17p), alemtuzumab showed higher ORR (64% vs. 20%) and longer median PFS (11 months vs. 2 months). After a median follow up of 25 months, median OS was not reached for either

treatment arm; no significant difference in survival was reported between treatment arms.¹¹¹ Alemtuzumab was associated with higher incidence of infusion-related events, cytomegalovirus (CMV) infections and grade 3 or 4 neutropenia (41% vs. 25%) compared with chlorambucil. Alemtuzumab in combination with FCR was also active as a first-line treatment in patients with del(17p).¹¹² While alemtuzumab is no longer commercially available, it may be obtained for clinical use. Alemtuzumab is not recommended as a first-line treatment option except for CLL with del(17p) when ibrutinib is not deemed to be appropriate.

Obinutuzumab is a glycoengineered, humanized, type II antibody targeted against CD20. The safety and efficacy of obinutuzumab in combination with chlorambucil for previously untreated CLL in patients with coexisting conditions was evaluated in the phase III randomized trial (CLL11 trial).⁹⁹ In this trial, 781 patients with comorbidities (defined as CIRS score >6 or an estimated creatinine clearance [CrCl] of 30 to 69 mL/min) were randomized to receive chlorambucil (n = 118), obinutuzumab plus chlorambucil (n = 333) or rituximab plus chlorambucil (n = 330). The combination of obinutuzumab-chlorambucil and rituximab-chlorambucil resulted in significant improvement in the median PFS compared to chlorambucil alone (26.7 months, 16.3 months, and 11.1 months respectively for obinutuzumab-chlorambucil, rituximab-chlorambucil and chlorambucil alone; $P < .001$). The survival benefit was seen in all of the subgroups except in patients with del(17p). The combination of obinutuzumab plus chlorambucil also resulted in higher ORR (78.4% vs. 65.1%), CR rate (20.7% vs. 7.0%) and significantly prolonged of median PFS (26.7 months vs. 15.2 months; $P < .001$) compared to rituximab plus chlorambucil.⁹⁹ The most frequent grade 3 or higher toxicities with obinutuzumab-chlorambucil included neutropenia (35%), infusion-

related reactions (21%), thrombocytopenia (11%) and infections (11%).⁹⁹ The most frequent grade 3 or higher toxicities with rituximab plus chlorambucil included neutropenia (28%) and infections (14%). The results of the CLL 11 study established obinutuzumab plus chlorambucil as the new standard of care for both elderly patients and for patients with comorbid conditions, lacking del(17p).⁹⁹ Based on the results of this study, obinutuzumab in combination with chlorambucil was FDA approved for the treatment of untreated CLL/SLL.

The efficacy of obinutuzumab monotherapy in patients with untreated CLL was demonstrated in the phase II GAGE study.¹¹³ In this trial, 80 patients with intact organ function and ECOG PS <3 were stratified to 2 different obinutuzumab doses (1,000 mg vs. 2,000 mg). The median age was 67 years. Obinutuzumab at 2000 mg resulted in higher ORR (assessed at 2 months after treatment according to the IWCLL criteria) than obinutuzumab at 1000 mg (67% and 49% respectively; $P = .08$).¹¹³ Infusion related reaction was the most frequent grade 3 or 4 adverse event in both treatment arms. Additional studies are warranted to determine the durability of response and long-term side effects obinutuzumab monotherapy in patients with untreated CLL.

Ofatumumab, a fully human CD20 monoclonal antibody, initially approved for the treatment of CLL refractory to fludarabine and alemtuzumab, was also evaluated as a first-line treatment for patients with untreated CLL who were considered inappropriate for fludarabine-based therapy due to advanced age and/or co-morbidities.¹¹⁴ In this multicenter open-label phase III study, 447 patients were randomized to ofatumumab plus chlorambucil vs. chlorambucil monotherapy. With a median follow-up of 29 months, the PFS was significantly longer for patients treated with ofatumumab plus chlorambucil compared to chlorambucil monotherapy (22.4 months vs. 13.1 months; $P < .001$).¹¹⁴ Ofatumumab plus chlorambucil also resulted in higher ORR

(82% vs 69%, $P = .001$) and superior CR rate (12% vs 1%) compared to chlorambucil alone. The median OS was reached in both arms. Based on the results of this study, the FDA approved ofatumumab plus chlorambucil for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.

A number of critical signaling pathways including the B-cell receptor (BCR), CXCR4/5, CD40, integrin, and IL-6 that signal via phosphatidylinositol 3-kinase (PI3K), Bruton's tyrosine kinase (BTK), and/or spleen tyrosine kinase (SYK) are implicated in the pathogenesis of CLL.^{115,116} Novel small molecule inhibitors targeting these kinases have been evaluated in clinical trials for the treatment of patients with CLL.

Ibrutinib is a covalent binding, irreversible inhibitor of BTK, initially approved for relapsed or refractory CLL (in patients who have received at least one previous therapy), was also evaluated in patients with untreated CLL including those with del(17p).¹¹⁷⁻¹¹⁹ In an open label multicenter phase Ib/II study of patients over the age of 65 ($n = 31$; median age 71 years [range 65–84]; 74% of patients were 70 years or older), ibrutinib (420 mg) resulted in an ORR of 71% (13% CR, 3% nodular PR and 55% PR).¹¹⁷ The median follow-up was 22 months. The responses were independent of the presence of high-risk features; however, the frequency of patients with del(17p), del(11q), or elevated beta-2-microglobulin was relatively low in this study.¹¹⁷ The ORR of 84% as reported in an independent evaluation of efficacy data at 3 years following initiation of therapy confirmed the durability of responses with ibrutinib in untreated CLL.¹¹⁸ In another open-label study of 29 patients (15 treatment-naïve patients) with del (17p), ibrutinib resulted in a nodal response rate of 82% at 6 months in treatment-naïve patients.¹¹⁹ The median follow-up was 9 months. Grade ≥ 3 non-hematological toxicities

were reported in 14% of patients. Ibrutinib was recently approved for first-line therapy in patients with del(17p). Unlike chemotherapy, ibrutinib causes early mobilization of lymphocytes into the blood which in the setting of clinical improvement should not be mistaken for progressive disease.^{77,79} While lymphocytosis can sometimes be profound, clinical consequence (i.e. leukostasis) is extremely rare and in general therapy should be continued. Slow or incomplete resolution of lymphocytosis does not appear to impact outcome as measured by PFS.⁷⁹ See "*Special Considerations for the Use of BCR Inhibitors (Ibrutinib and Idelalisib)*" in the guidelines.

Idelalisib (the isoform-selective oral inhibitor of PI3K-delta) in combination with rituximab is approved for the treatment of relapsed or refractory CLL in patients who received at least one previous therapy. The efficacy of idelalisib monotherapy or in combination with rituximab was also demonstrated in older patients (≥ 65 years) with previously untreated CLL and adverse risk factors.^{120,121} In the preliminary analysis of a phase II study ($n = 37$; median age 70 years), idelalisib had substantial monotherapy activity resulting in an ORR of 81% (33% PR and 48% PR with lymphocytosis).¹²⁰ The most frequent grade 3 or higher treatment-related adverse events were rash (3%), diarrhea (3%), pneumonia (5%), transaminase elevation (8%), anemia (5%), and neutropenia (20%). In another phase II study ($n = 64$; median age 71 years), the combination of idelalisib and rituximab induced ORR in 97% of patients (78% PR and 19% CR).¹²¹ Diarrhea/colitis (42%), pneumonia (19%), rash (13%), dehydration (8%), dyspnea (5%) and respiratory failure (5%) were the most frequent grade 3 or higher treatment-related adverse events. Similar early lymphocytosis as described with ibrutinib can occur with idelalisib and should be managed similarly.^{78,122} See "*Special Considerations for the Use of BCR Inhibitors (Ibrutinib and Idelalisib)*" in the guidelines.

Relapsed or Refractory Disease

The current standards of care for relapsed or refractory CLL are ibrutinib monotherapy and idelalisib plus rituximab.

Ibrutinib showed remarkable monotherapy activity with favorable toxicity profile in patients with relapsed/refractory B-cell malignancies.¹²³ The safety and efficacy of ibrutinib in relapsed or refractory CLL/SLL was first evaluated in a phase Ib/II study (n = 85; 51 patients received 420 mg and 34 patients received 840 mg).⁷⁷ The majority of patients were considered to have high-risk features (advanced-stage disease, del(17p) and del(11q) were present in 65%, 33% and 36% of patients respectively). The ORR was the same (71%) in the two dose groups. Among the subgroup of 28 patients with del(17p), the ORR was 68% (CR in 3.5%). PR with lymphocytosis was observed in 20% and 15% of patients in the two dose groups, (420 mg and 840 mg) respectively. The estimated PFS and OS at 26 months was 75% and 83%, respectively. The most common grade 3 or 4 adverse events included neutropenia (15%), pneumonia (12%), sinusitis (5%) and hypertension (5%).

In the subsequent phase III randomized study (RESONATE), 391 patients with previously treated CLL were randomized to monotherapy with ibrutinib (420 mg once daily) or ofatumumab.¹²⁴ Majority of patients had advanced stage disease and high-risk features including del(17p), del(11q) or beta-2 microglobulin (>3.5 mg/L). At a median follow-up of 9.4 months, ibrutinib significantly prolonged PFS (median not reached vs. 8.1 months for ofatumumab) and OS (HR for death in the ibrutinib group was 0.43; $P=$.005; 57% reduction in the risk of death). Among patients with del(17p), median PFS was not reached with ibrutinib, compared with a median PFS of 5.8 months with ofatumumab. At 12 months, the OS rate was 91% and 81%, respectively for ibrutinib and ofatumumab.¹²⁴ The ORR was also significantly higher with ibrutinib (42% vs. 4%; $P < .001$). The most frequent nonhematologic adverse

events were mild (Grade 1-2) diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. The updated results of this study also confirmed that ibrutinib significantly improved PFS, OS, and ORR compared to ofatumumab in patients with CLL/SLL who had received at least one prior therapy.¹²⁵ With median follow-up of 16 months, the ORR (90% vs. 25%; $P < .0001$), median PFS (not reached vs. 8.1 months for ofatumumab; $P < .0001$) and OS rates (18-month OS rates were 85% and 78% respectively) were significantly better for ibrutinib. The results of the phase II study (RESONATE-17) further confirmed the efficacy of ibrutinib in patients with relapsed or refractory CLL with del(17p).¹²⁶ At a median follow-up of 13 months, the ORR and PFS rate were 82.6% and 79.3 % respectively.

Ibrutinib was approved by the FDA for the treatment of patients with CLL who received at least one previous therapy and for first-line therapy in patients with del(17p) CLL.

Idelalisib, the isoform-selective oral inhibitor of PI3K-delta, demonstrated promising clinical activity in phase I-II studies in patients with relapsed/refractory CLL, both as monotherapy and in combination with rituximab.^{78,122} In the multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with either idelalisib (150 mg) or placebo.⁷⁸ Majority of the patients (78%) were 65 years or older, 40% had moderate renal dysfunction (creatinine clearance, <60 ml/min), 35% had poor bone marrow function (grade 3 or higher cytopenias) and 85% had a score CIRS score > 6. At the first planned interim analysis, the study was stopped early owing to the overwhelming efficacy of idelalisib plus rituximab.⁷⁸ At 24 weeks, the PFS rate was 93% and 46%, in the idelalisib group and placebo group respectively. Among patients with relapsed CLL with co-existing conditions, idelalisib plus rituximab significantly improved ORR (81% vs.

13%; $P < .001$), PFS (not reached in the idelalisib group vs. 5.5 months in the placebo group) and OS at 12 months (92% vs. 80%; $P = .02$), compared to rituximab plus placebo. Grade 3 or 4 adverse events (pneumonia, pyrexia and febrile neutropenia) were reported in 40% of patients in the idelalisib group and 35% in the placebo group. The second interim analysis of this study also confirmed the superior safety and efficacy of idelalisib plus rituximab in terms of ORR, OFS and OS.¹²⁷ Idelalisib plus rituximab also retained efficacy in patients with high-risk features such as del(17p) or *TP53* mutations, unmutated *IGHV*, *ZAP70* and CD38 expression and beta-2 microglobulin (>4 mg/L).¹²⁸ Idelalisib in combination with rituximab was recently FDA approved for the treatment of relapsed CLL in patients for whom rituximab monotherapy would be considered appropriate due to the presence of other co-morbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥ 3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents).

The FCR regimen was shown to induce high response rates in the relapsed/refractory disease setting.^{129,130} In a phase II study evaluating FCR in patients with relapsed/refractory CLL (n=284; median 2 prior therapies, range 1–10), the ORR was 74% with a CR rate of 30%.¹³⁰ The median PFS was 21 months and the estimated median survival was 47 months. The subgroup of patients with fludarabine-refractory disease (n=54) had significantly lower ORR (56% vs. 79%; $P < 0.001$) and CR rate (7% vs. 39%; $P < 0.001$) compared with fludarabine-sensitive patients; the median PFS (8 months vs. 28 months; $P < 0.001$) and OS (38 months vs. 52 months; $P < 0.05$) was also significantly decreased among patients with fludarabine-refractory CLL.¹³⁰ In addition, the subgroup of patients (n=20) with chromosome 17 abnormalities (based on standard karyotyping) had the worse outcomes

with an ORR of 35% (no CR), median PFS of 5 months, and median survival of only 10.5 months. The investigators concluded that the patients most appropriate for therapy with FCR were those who were fludarabine sensitive, with no chromosome 17 abnormalities, and with fewer prior therapies (<4 prior regimens).¹³⁰ The most common adverse events with FCR were hematologic toxicities, including grade 3 or 4 neutropenia associated with 56% of treatment cycles and grade 3 or 4 thrombocytopenia in 19.5% of cycles. Pneumonia or sepsis was reported in 16% of patients.¹³⁰

The phase III randomized REACH trial compared 6 cycles of FCR with 6 cycles of FC in patients with CLL at first relapse (n=552).¹³¹ In this study, patients were excluded if they received prior FC (as a combination) or prior rituximab; moreover, patients were required to be fludarabine sensitive. After a median follow-up time of 25 months, patients in the FCR arm had significantly improved median PFS (based upon investigator assessment) compared with the FC arm (31 months vs. 21 months; $P < 0.001$). The median PFS as assessed by an independent review committee also showed a significant benefit with FCR compared with FC (27 months vs. 22 months; $P = 0.022$). Based on independent review committee evaluation, both the ORR (61% vs. 49%; $P < 0.005$) and CR rate (9% vs. 3%; $P < 0.005$) were significantly higher with the FCR regimen.¹³¹ At the time of follow up, OS was not significantly different between treatment regimens. Based on the results of this trial, the FDA approved rituximab in combination with fludarabine and cyclophosphamide for patients with previously treated CD20-positive CLL.

The combination of pentostatin and cyclophosphamide (PC) with or without rituximab (R) showed significant activity in patients with relapsed or refractory CLL, including in patients with fludarabine-refractory disease.^{132,133} In a small study in patients with

relapsed/refractory CLL (n=23; median 3 prior therapies, range 1–5), the PC combination resulted in an ORR of 74% and CR rate of 17%; the ORR among patients with fludarabine-refractory disease was 77%.¹³³ In a study that evaluated the PCR regimen, the ORR and CR rate in the subgroup of patients with previously treated CLL (n=32) was 75% and 25%, respectively; the ORR among patients with fludarabine-refractory disease was 75%.¹³² Thus, the response rates with the PC and PCR regimens appeared similar. However, based on a historical retrospective comparison, the median duration of response (25 months vs. 7 months) and median survival (44 months vs. 16 months) were longer with the PCR regimen compared with the PC regimen.¹³²

Oxaliplatin, fludarabine, cytarabine and rituximab (OFAR) was shown to have significant activity in relapsed/refractory CLL (including patients with high-risk features such as 17p or 11q deletion) and Richter's transformation.^{134,135} In a phase I-II trial, of patients with fludarabine-refractory CLL (n=30) and those with Richter's transformation (n=20), OFAR resulted in an ORR of 50% and 33% respectively, in patients with Richter's transformation and fludarabine-refractory CLL.¹³⁴ The median response duration was 10 months. The ORR in the subgroup of patients aged 70 years or older (n=14) was 50%. In addition, responses were achieved in seven (35%) of 20 patients with del(17p) and two (29%) of seven patients with del(11q).¹³⁴ In the subsequent phase I-II study (67 patients with relapsed/refractory CLL and 35 patients with RS), a modified OFAR regimen with reduced dose cytarabine also resulted in ORR of 38.7% (6.5% CR) in patients with RS and 50.8% (4.6% CR) in those with relapsed/refractory CLL. The median survival durations were 6.6 and 20.6 months, respectively.¹³⁵ Cytopenias were the most common hematologic toxicities. Allogeneic SCT as post-remission

therapy in patients treated with modified OFAR was associated with prolonged survival.¹³⁵

The German CLL Study Group conducted a phase II trial combining bendamustine and rituximab for patients with relapsed CLL (n=78; median 2 prior therapies, range 1–5) which resulted in an ORR of 59% and CR rate of 9%.¹³⁶ The ORR among the subgroup (n=22) with fludarabine-refractory disease was 45.5%. Among the patients with del(17p) (n=14), only 1 patient (7%) responded (with a CR). After a median follow up of 24 months, the median PFS and OS for all patients was 15 months and 34 months, respectively. Patients with del(17p) had the worse outcomes with a median PFS of 7 months and median survival of 16 months.¹³⁶ The most common grade 3 or 4 adverse events included hematologic toxicities (50% of patients) and infections (13%; all grade 3 events).¹³⁶ An ongoing phase III randomized trial is evaluating outcomes with BR compared with R-chlorambucil as first-line or second-line therapy in patients with CLL who are not suitable for fludarabine-based chemoimmunotherapy (due to older age or comorbid conditions). In an interim analysis of this trial, data from 126 patients (median age 74 years, range 44–91) were available for evaluation (BR, n=58; R-chlorambucil, n=68).¹⁰⁷ Among the patients who received second-line therapy (n=51; relapse occurred >12 months since last dose of first-line treatment), the ORR was 89% in the BR group (CR in 11%) and 83% (CR in 4%) in the R-chlorambucil group.¹⁰⁷

High-dose methylprednisolone (HDMP) combined with rituximab was shown to be well tolerated and an active therapy for patients with refractory CLL, including in those with unfavorable prognostic features. In several small studies, treatment with HDMP combined with rituximab resulted in ORR of 78-93% with CR in 14% to 36% of patients; median PFS (or time to progression) was 7-15 months, and

one study reported a median survival of 20 months.¹³⁷⁻¹³⁹ In addition, this regimen was shown to be active in patients with fludarabine-refractory disease and/or del(17p).^{137,138} The regimen was associated with infectious complications (including opportunistic fungal infections) in about 30% of patients,^{137,139} which may necessitate adequate antiinfective prophylaxis and close monitoring for early signs of infections.

Initial phase II studies of lenalidomide monotherapy for patients with relapsed/refractory CLL showed ORRs of 32% to 47% and CR rates of 7% to 9%.^{140,141} Among the subgroup of patients with del(11q), the ORR was 39% to 47%; the ORR in the small subgroup of patients with del(17p) was only 13%.^{140,141} Tumor flare reactions occurred in 58% of patients (grade 3 or 4 in 8%).¹⁴⁰ The most common grade 3 or 4 toxicities included neutropenia (70%), thrombocytopenia (45%), anemia (18%) and febrile neutropenia (15%).¹⁴⁰ Lenalidomide was administered using different dosing schedules in these earlier studies. In one study, patients initially received lenalidomide at the 25 mg daily dose given intermittently (21 days of a 28-day cycle), which is the dosing schedule used for multiple myeloma; due to tumor lysis syndrome observed in the first patients on the study, the starting dose was reduced to 5 mg daily with subsequent dose escalation up to 25 mg daily.¹⁴⁰ In the other study, patients initially received lenalidomide at a dose of 10 mg daily given continuously for 28 days of a 28-day cycle; the dose was escalated up to a maximum of 25 mg daily.¹⁴¹ No tumor lysis was reported in this latter study. Studies showed that in patients with CLL, the “standard” 25 mg dose of lenalidomide used in patients with multiple myeloma resulted in excessive toxicity (tumor flare, tumor lysis and myelosuppression) when given as the initial dose.^{88,140,142} More recently, lenalidomide was investigated in combination with rituximab in patients with relapsed/refractory CLL. A phase II study evaluated lenalidomide

(initial dose 10 mg daily started on day 9 of cycle 1; given 28 days of a 28-day cycle) combined with rituximab (375 mg/m² weekly for 4 weeks in cycle 1, then on day 1 of cycles 3–12) in patients with relapsed/refractory CLL (N = 59; median 2 prior regimens).¹⁴³ The ORR was 66% with CR in 12%; all CRs were observed after 12 or more cycles of therapy. The median time to treatment failure was 17 months for all patients. The median OS was reached, with an estimated 3-year OS rate of 71%. Among the subgroup of patients with del(17p) (n = 15), the ORR was 53%, which was not significantly different from the 70% ORR among patients without del(17p). However, the subgroup of patients considered fludarabine refractory (n = 12) had decreased ORR compared with those who were sensitive (33% vs. 70%; P=0.04). In addition, patients with del(17p) who were also fludarabine refractory had the worse survival outcomes, with a median OS less than 10 months. The most common grade 3 or 4 toxicity included neutropenia (74%), thrombocytopenia (34%), and infections or febrile episodes (24%). Tumor flare reactions occurred in 27% of patients, but were all grade 1 or 2 events.¹⁴³

The efficacy of alemtuzumab in patients with fludarabine-refractory CLL with del(17p) or *TP53* abnormalities was demonstrated in several studies.¹⁴⁴⁻¹⁴⁶ In a phase II study, alemtuzumab induced significant responses in patients who were refractory to fludarabine-based therapy (n=93), with an ORR of 33% (CR 2%).¹⁴⁴ The median time to progression was 4.7 months for all patients (9.5 months for responders) and the median OS was 16 months (32 months for responders).¹⁴⁴ Subcutaneous administration of alemtuzumab was also as effective and safe as intravenous alemtuzumab in patients with advanced-stage relapsed or refractory CLL.¹⁴⁷⁻¹⁵⁰ The most common grade 3-4 toxicities with alemtuzumab in patients with heavily pretreated, relapsed or refractory disease included myelosuppression and infections.^{144,149} In a

retrospective analysis that included 202 patients with pretreated CLL and del(17p), alemtuzumab was associated with favorable ORR (32%), median PFS and OS (6.2 months and 21 months, respectively).¹⁵¹ It should be noted that bulky lymphadenopathy does not typically respond well to alemtuzumab monotherapy in patients with refractory CLL.^{144,151}

Alemtuzumab-based chemoimmunotherapy regimens also demonstrated promising results in patients with relapsed/refractory CLL. In phase II and III studies, alemtuzumab in combination with fludarabine resulted in ORR of 82% to 85% and CR rates of 13% to 30% in relapsed CLL.^{152,153} In the phase III randomized trial (n=335), the median PFS was significantly longer with fludarabine and alemtuzumab compared with fludarabine alone (24 months vs. 16.5 months; $P=0.003$); infection rates were high, with 41% of patients in the alemtuzumab arm experiencing infections (any grade, and including CMV reactivation) compared with 35% in the fludarabine arm.¹⁵³ Alemtuzumab in combination with FC also resulted in an ORR of 68% (CR 22%) in patients with previously treated CLL (n=56). Serious adverse events related to infections were reported in about 20% of patients.¹⁵⁴ Alemtuzumab in combination with rituximab also showed promising results. In a phase II study (n= 40), alemtuzumab (continuous infusion followed by subcutaneous administration) in combination with rituximab resulted in ORR of 53% (CR 18%); infections (any grade, and including CMV reactivation) were reported in 28% of patients.¹⁵⁵ A more intensive chemoimmunotherapy regimen that combines cyclophosphamide, fludarabine, alemtuzumab and rituximab (CFAR) was evaluated in a phase II study in patients with heavily pretreated relapsed/refractory CLL with high-risk features (n=80; median 3 prior therapies, range 1-14; 39% fludarabine-refractory).¹⁵⁶ The ORR was 65% (CR 29%); median PFS and OS was 11 months and 17 months, respectively.¹⁵⁶ This regimen was

associated with a high rate of grade 3-4 infections (46%) and was not as active in the subgroup of patients with del(17p) (CR 14%; median PFS 3 months) or fludarabine-refractory CLL (CR 10%; median PFS 7 months).

CMV reactivation can occur in about 10%-25% of patients with relapsed/refractory CLL treated with alemtuzumab.^{144,149,151,157,158} It is therefore important to monitor for CMV antigenemia during alemtuzumab therapy. Appropriate anti-infective prophylaxis and routine monitoring for early signs of infectious complications are warranted when administering alemtuzumab-containing regimens.

Ofatumumab is a fully human CD20 monoclonal antibody with activity in patients with CLL refractory to fludarabine and alemtuzumab or in patients for whom alemtuzumab is contraindicated due to bulky lymphadenopathy.¹⁵⁹ In the final analysis from the pivotal international clinical trial, which included data from 206 patients with fludarabine- and alemtuzumab-refractory (FA-ref; n=95) CLL or patients with fludarabine-refractory CLL with bulky lymphadenopathy (BF-ref; n=111), ofatumumab therapy resulted in an ORR of 51% in the FA-ref and 44% in the BF-ref patients.¹⁶⁰ The median PFS was 5.5 months for both groups, and the median OS was 14 months and 17 months for the FA-ref and the BF-ref groups, respectively. The most common \geq grade 3 adverse events were infections (24%) and neutropenia (12%). An ad hoc retrospective analysis of patients with FA-ref CLL (n=96) and BF-ref CLL (n=111) showed that ofatumumab was also effective and well tolerated in patients with FA-ref CLL and previous rituximab exposure.¹⁶¹ The ORR was 43%, 44%, and 53% respectively for CLL with previous rituximab exposure, rituximab-refractory CLL, and rituximab-naïve CLL. The median PFS was 5.3, 5.5, and 5.6 months, respectively and median overall survival was 15.5, 15.5, and 20.2

months, respectively. Ofatumumab is approved for the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

Obinutuzumab has monotherapy activity in patients with heavily pretreated relapsed/refractory CLL. In a phase II study (GAUGIN study) of 20 patients, obinutuzumab at a fixed dose of 1000 mg resulted in a best ORR of 30%; median PFS and duration of response were 10.7 months and 8.9 months, respectively.¹⁶² A subset analysis of the CLL11 study showed that the combination of obinutuzumab plus chlorambucil was also active in patients with CLL refractory to prior treatment with chlorambucil.¹⁶³ Among the 30 patients who crossed over to obinutuzumab plus chlorambucil, clinical response was seen in 87% of patients (77% PR, 7% CR and 3% incomplete CR). The median PFS from start of crossover treatment was 17.2 months.

Allogeneic hematopoietic stem cell transplant (HSCT) was evaluated to improve the prognosis in patients with advanced disease and those with poor-risk features.¹⁶⁴⁻¹⁷⁰ In a retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT), allogeneic HSCT induced long-term remission in patients with del(17p).¹⁶⁹ At a median follow-up period of 39 months, 3-year PFS and OS rates were 37% and 44%, respectively. The final results of the prospective multicenter trial (GCLLSG CLL3X study) also showed that nonmyeloablative allogeneic HSCT can induce sustained MRD-negative event-free survival (EFS) in a significant proportion of patients with poor-risk CLL (defined as refractoriness or early relapse to purine analog-containing therapy, relapse after autologous SCT, disease progression with presence of unfavorable genomic abnormalities).¹⁷⁰ The 4-year EFS and OS rates for patients who underwent HSCT in this study (n=90) was 42% and 65%, respectively; 52% of patients had MRD negativity at 12 months post-HSCT.¹⁷⁰ The 4-year non-relapse mortality rate was 23%. The 4-year EFS and OS rates for the subgroup of patients with del(17p)

(n=13) was 45% and 59%, respectively, and was not significantly different from the survival rates of patients without del(17p). Moreover, 6 of 13 patients (46%) with del(17p) achieved durable MRD-negative remissions.¹⁷⁰

It is understood that studies involving allogeneic HSCT are subject to strong selection biases. Nonetheless, available evidence from non-randomized clinical studies suggest that allogeneic HSCT may be an effective treatment option for patients refractory to chemoimmunotherapy or who develop recurrence within 12 months after purine analog treatment.¹⁷¹

Assessment of Functional Status and Comorbidity

CLL is diagnosed mainly in older adults, with a median age of 72 years at diagnosis. Approximately 70% of patients are diagnosed at age ≥ 65 years and 40% of patients are diagnosed at age ≥ 75 years.¹⁷²

Comorbidities are frequently present in older patients. In addition, organ function and bone marrow reserve also decline with advancing age.

Although chemoimmunotherapy is now considered the standard of care for younger or fit older patients, it is often not well tolerated in older patients due to decline in organ function, reduced bone marrow reserve and/or the presence of comorbidities.¹⁷³ In the first phase III randomized study (CLL5) that evaluated first-line chlorambucil vs. fludarabine in a cohort of older patients (≥ 65 years) with untreated CLL, 65% of patients presented with at least one comorbidity, and about a third of patients had two or more comorbidities at the time of enrollment.⁸⁵ In this trial, the presence of multiple comorbidities was a negative prognostic factor independent of disease stage or age. In multivariate analysis, elevated serum beta-2-microglobulin and the presence of 2 or more comorbidities were significant independent predictors of shorter PFS and OS.⁸⁵ Several retrospective studies also reported on the negative

impact of comorbidities on patient outcomes in CLL.¹⁷⁴⁻¹⁷⁶ The most common comorbidities reported include hypertension (19–53%), coronary artery disease (7–24%), hyperlipidemia or lipometabolic disease (16–38%), and diabetes mellitus (10–21%).¹⁷⁴⁻¹⁷⁶

These findings underscore the need to assess comorbidities, in addition to patient age and performance status, prior to treatment selection. The tolerability of a treatment regimen relative to a patient's physical fitness is an important consideration in the management of CLL. Cumulative Illness Rating Scale (CIRS), Charlson Comorbidity Index, and the NCI Comorbidity Index are some of the scoring systems that can be used to assess comorbidities in patients with CLL. CIRS in combination with CrCI was used by the German CLL Study Group to assess the overall fitness of patients enrolled in clinical trials.^{49,177}

NCCN Recommendations

Localized SLL (Ann Arbor stage I)

Locoregional radiation therapy (RT) 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 (Ann Arbor stage II–IV).

SLL (Ann Arbor 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. A “watch and wait” approach is often appropriate for patients with early stage, low-risk disease (Rai stage 0; Binet A) in the absence of disease symptoms.

Patients with Binet B or intermediate-risk disease (Rai stage I or II) may benefit from therapy if they show evidence of progressive disease or become symptomatic.⁴ Patients with advanced stage or high-risk CLL (Binet C; Rai stage III–IV) with progressive cytopenia require immediate treatment. Selected patients with mild, stable cytopenia may continue to be observed.

Absolute lymphocyte count alone is not an indication for treatment unless it is above 200 to 300 × 10⁹/L or symptoms related to leukostasis occur. Standard indications for initiating treatment include the following⁴: significant disease related constitutional symptoms including severe fatigue, weight loss, night sweats and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); progressive anemia or thrombocytopenia; or autoimmune anemia/thrombocytopenia unresponsive to corticosteroids. Asymptomatic patients should be observed until such indications (as mentioned above) become apparent.

Given the incurability of the disease, the NCCN Guidelines recommend enrollment in clinical trials, when locally available, as the preferred option for all patients with indications for treatment. In the absence of suitable clinical trials, the treatment recommendations included in the NCCN Guidelines are based on patient's age or functional status (comorbidity index/performance status) as well as the presence or absence of del(17p) and/or del(11q).

Management of Frail Patients with Significant Comorbidity

Obinutuzumab plus chlorambucil (category 1),⁹⁹ ofatumumab plus chlorambucil¹¹⁴ and rituximab plus chlorambucil^{97,98} are the preferred treatment options for frail patients with significant comorbidities that preclude treatment with purine analogs. Other options include monotherapy with obinutuzumab, rituximab, chlorambucil or pulse

corticosteroids.^{85,95,113} See “Suggested Treatment Regimens: Frail Patient, Significant Comorbidity (not able to tolerate purine analogs)” in the guidelines for a list of other suggested regimens.

Management of Patients with Adequate Functional Status

Patients with adequate functional status can be treated with more active or intensive therapies, and should be evaluated for cytogenetic abnormalities by FISH. Patient age and the presence or absence of del(17p) and/or del(11q), should then help to direct treatment options, as shown below.

CLL without del(17p) or del(11q)

First-line Therapy

For patients 70 years or older and younger patients with significant comorbidities, obinutuzumab plus chlorambucil (category 1)⁹⁹ is the preferred regimen followed by ofatumumab plus chlorambucil,¹¹⁴ rituximab plus chlorambucil^{97,98} or bendamustine with or without rituximab.^{93,94,106} Other options include obinutuzumab monotherapy,¹¹³ fludarabine with or without rituximab,^{58,85,100} chlorambucil,⁸⁵ rituximab⁹⁵ or cladribine (for rare patients with CNS disease).¹⁷⁸

In patients younger than 70 without significant comorbidities fludarabine-based chemoimmunotherapy has emerged as the standard of care.^{49,58,106} A randomized comparison of FCR versus PCR demonstrated a higher CR rate for FCR but the ORR and survival were no different between the regimens.¹⁰⁵ Data from the final analysis of the CLL10 study confirmed the superiority of FCR over bendamustine plus rituximab in patients 70 years or younger, without significant comorbidities.¹⁰⁶ Bendamustine plus rituximab is a reasonable alternative for 70 years or older who are otherwise eligible for chemoimmunotherapy.^{106,108}

For patients 70 years or younger, without significant comorbidities, the NCCN Guidelines recommend purine analog-based chemoimmunotherapy (FCR, FR, PCR) or bendamustine with or without rituximab. See “Suggested Treatment Regimens: CLL without del(17p) or del(11q)” in the guidelines for a list of other suggested regimens.

Although an oral formulation of fludarabine was investigated¹⁷⁹⁻¹⁸¹ and is approved by the FDA for the treatment of patients with CLL (who have not responded to or progressed after treatment with at least one alkylating agent), its use in combination regimens has not yet been established in patients with CLL. Moreover, no prospective randomized trials evaluated the activity and safety of the oral formulation compared with IV fludarabine. Therefore, the NCCN Guidelines cannot recommend the appropriate use of oral fludarabine at this time.

Second-line Therapy

Based on the recent FDA approvals, ibrutinib (category 1)¹²⁴ and idelalisib ± rituximab^{78,182} are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities.

For patients 70 years or older and younger patients with comorbidities, the NCCN Guidelines included reduced-dose FCR or PCR, bendamustine with or without rituximab, HDMP or chlorambucil with rituximab, monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or dose-dense rituximab as alternative options.

For patients younger than 70 years without significant comorbidities, the NCCN Guidelines included chemoimmunotherapy (FCR, PCR,

bendamustine with or without rituximab, fludarabine with alemtuzumab, CHOP with rituximab, OFAR), monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or HDMP with rituximab as alternative options. Allogeneic HSCT can be considered for select patients (without significant comorbidities) after re-induction of remission.

See “*Suggested Treatment Regimens: CLL without del(17p) or del(11q)*” in the guidelines for a list of other suggested regimens

CLL with del(17p)

Outcomes remain poor with currently available chemoimmunotherapy regimens. Based on the recent FDA approval, ibrutinib is included as an option for first-line therapy and for relapsed or refractory CLL.^{117-119,124}

Enrollment in an appropriate clinical trial is recommended for patients with del(17p). In the absence of appropriate clinical trials in the patient's local area, suggested first-line therapy options include ibrutinib, chemoimmunotherapy (FCR or FR, HDMP plus rituximab) or alemtuzumab with or without rituximab. The efficacy of ibrutinib in relapsed or refractory CLL with del(17p) patients exceeds the results of alternative regimens in the upfront setting and should be considered as the best choice in the absence of a contraindication to give this treatment.

Patients with response to first-line therapy should be considered for allogeneic HSCT, if they are eligible. However, the role of allogeneic HSCT in the up-front setting such as this is evolving with the introduction of new targeted therapies. Patients with a response following allogeneic HSCT can either be observed or enrolled in clinical trials.

Patients with no response to first-line therapy, patients who respond to first-line therapy but are not eligible for allogeneic HSCT and for those with no response to allogeneic HSCT should be enrolled in clinical trials or be treated with second-line therapy for relapsed or refractory disease. Ibrutinib and idelalisib ± rituximab are the preferred options for relapsed or refractory disease.

See “*Suggested Treatment Regimens: CLL with del(17p)*” in the guidelines for a list of other suggested regimens.

CLL with del(11q)

Outcomes are more favorable for patients treated with alkylating agent-based chemoimmunotherapy regimens.

For patients 70 years or older and younger patients with comorbidities, preferred first-line treatment options include obinutuzumab plus chlorambucil (category 1),⁹⁹ followed by ofatumumab plus chlorambucil,¹¹⁴ rituximab plus chlorambucil^{97,98} or bendamustine with or without rituximab.^{93,94,106} Other options include cyclophosphamide and prednisone with or without rituximab, chlorambucil or rituximab.

For patients younger than 70 years without significant comorbidities, first-line treatment options include FCR, bendamustine with or without rituximab or PCR.

Patients who achieved CR to first-line therapy can either be observed until disease progression or enrolled in clinical trials. Patients with PR to first-line therapy should be considered for allogeneic HSCT, if they are eligible. However, the role of allogeneic HSCT is evolving with the introduction of new targeted therapies. Following transplant, treatment options are similar to those described for patients with del(17p).

Patients with no response to first-line therapy and patients with PR to first-line therapy but are not eligible for allogeneic HSCT should be enrolled in clinical trials or can be treated with second-line therapy for relapsed or refractory disease. Ibrutinib and idelalisib ± rituximab are the preferred options for relapsed or refractory disease. See “Suggested Treatment Regimens: CLL with *del(11q)*” in the guidelines for a list of other suggested regimens based on the patient's age and the presence or absence of significant comorbidities.

Histologic Transformation

About 2% to 10% of patients with CLL will develop Richter's transformation (histologic transformation to DLBCL or Hodgkin lymphoma) during the course of their disease and treatment.¹⁸³⁻¹⁸⁵ The incidence of histologic transformation increases with the number of prior regimens. Recent reports identified inactivation of NOTCH1 and disruption of TP53 and CDKN2A/B as possible genetic pathways involved in the pathogenesis of Richter's transformation.^{186,187}

Patients with Richter's transformation should be treated with chemoimmunotherapy regimens initially developed for DLBCL.^{188,189} OFAR and hyper-CVAD with rituximab were also used for the treatment of patients with Richter's transformation.^{134,135,190} Allogeneic HSCT can also be considered following a response to initial therapy in patients with Richter's transformation. In a non-randomized comparative analysis, the estimated cumulative 3-year survival rate was significantly higher (75%) for patients who underwent allogeneic HSCT after achieving CR or PR to initial therapy compared with those who responded to initial therapy but did not undergo allogeneic HSCT, or who underwent allogeneic HSCT for relapsed or refractory Richter's transformation (75% vs. 27% and 21%, respectively; $P=.019$).¹⁸⁸ HDT/ASCR may also be an appropriate therapy for patients with

Richter's transformation who have a response to initial therapy but are not a candidate for allogeneic HSCT due to age, co-morbidities, or lack of a suitable donor.¹⁹¹

Patients with Hodgkin histology should receive a standard regimen used for the treatment of Hodgkin lymphoma.

Other histologic transformations including CLL with increased prolymphocytes (CLL-PL) or accelerated CLL (presence of expanded proliferation centers or a high proliferation rate) are associated with a more aggressive disease course and optimal management was not established.

Supportive Care for Patients with CLL

Infections

Patients with CLL are susceptible to infectious complications due to the underlying disease as well as treatment with immunosuppressive agents. Infectious complications are influenced by the progressive reduction in immunoglobulin levels and are more common in previously treated patients.¹⁹² Hypoglobulinemia was shown to be present in about 40% of patients up to 3 years prior to diagnosis of CLL.¹⁹³ Heavily pretreated patients who become refractory to fludarabine have high susceptibility to developing serious infections. In a retrospective analysis, 89% of patients with fludarabine-refractory CLL developed infectious complications requiring hospitalization.¹⁹⁴ Administration of IVIG (for recurrent infections and if IgG levels <500 mg/dL), antiinfective prophylaxis and vaccinations are the main options available to minimize the possibilities of developing infectious complications.

In randomized studies, IVIG was associated with a significant decrease in the occurrence of infections but with no improvement in overall survival outcome.¹⁹⁵⁻¹⁹⁹ Antibacterial prophylaxis may be a useful

alternative option. Protein and conjugate vaccines were shown to induce better responses than plain polysaccharide vaccines.^{200,201} Some studies reported that histamine type-2 (H2) receptor blockers can enhance vaccine response.^{202,203}

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

Annual influenza vaccine and pneumococcal vaccine (every 5 years) is recommended for all patients.²⁰⁴ All live vaccines should be avoided. Patients with CLL tend to have poor response to influenza vaccine and should be counseled to exercise care during influenza season even with vaccination.

Hepatitis B virus (HBV) carriers with lymphoid malignancies have high risk of HBV reactivation and disease,²⁰⁵ especially for patients treated with CD20 monoclonal antibodies (e.g. rituximab, ofatumumab) or HDMP.²⁰⁶ Management recommendations for prevention of HBV reactivation (including surveillance and antiviral prophylaxis or pre-emptive therapy) are discussed in the NHL Guidelines section for overall Supportive Care.

Cytomegalovirus (CMV) reactivation is a well-documented infectious event in patients receiving treatment with alemtuzumab, occurring in up to 25% of patients.^{110,111,144,149,157,207} Although the standard approach to CMV monitoring and management remains under debate, current practices include the use of prophylactic ganciclovir (oral or IV) if CMV viremia is present prior to alemtuzumab therapy,²⁰⁸ or preemptive use of these drugs when the viral load is found to be increasing during therapy.^{209,210}

Clinicians should be aware of the high risk of CMV reactivation in patients with CLL treated with alemtuzumab-containing regimens. Monitoring for the presence of CMV antigens regularly using quantitative polymerase chain reaction (PCR) assays is an effective approach to the management of CMV reactivation.²¹¹ The NCCN Guidelines recommend routine surveillance for CMV viremia (every 2–3 weeks) during the treatment course with alemtuzumab and for 2 months following completion of treatment. Consultation with an infectious disease expert may be necessary.

Autoimmune Cytopenias

Autoimmune hemolytic anemia (AIHA), immune-mediated thrombocytopenia, also known as immune thrombocytopenic purpura (ITP) and pure red blood cell aplasia (PRCA) are the most frequent autoimmune cytopenias in patients with CLL.^{212,213} Bone marrow evaluation is recommended to confirm the diagnosis of autoimmune cytopenias.

AIHA is the most common form of autoimmune cytopenia. Although direct antiglobulin test (DAT) was used for the diagnosis of AIHA, most patients with AIHA have negative DAT; additional markers such as low haptoglobin and elevated reticulocyte and LDH are required to confirm the diagnosis of AIHA.²¹⁴ 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.²¹⁴⁻²¹⁷ 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.^{214,218} AIHA should not preclude the use of combination therapy containing fludarabine, and patients should be observed carefully. In the case of severe AIHA, fludarabine therapy should be discontinued and subsequent use of the agent should be avoided.

ITP in patients with CLL is associated with poorer survival independent of common clinical prognostic variables.²¹⁹ In a recent Italian study, high WBC count, unmutated *IGHV*, positive DAT and ZAP-70 positivity were associated with the development of ITP in patients with CLL.²¹⁹

AIHA and ITP can be managed with corticosteroids in most cases. IVIG, cyclosporine²²⁰ and splenectomy should be used in steroid-refractory cases. Rituximab was also effective for the treatment of patients with autoimmune cytopenias²²¹⁻²²⁷ More recently, synthetic thrombopoietin-like agents such as romiplostim and eltrombopag showed promising results in the treatment of thrombocytopenia associated with ITP.²²⁸⁻²³¹ Both romiplostim and eltrombopag are FDA-approved for the treatment of thrombocytopenia in patients with ITP that is refractory to steroids, IVIG and splenectomy.

PRCA is less common in patients with CLL. PRCA can be managed with corticosteroids, cyclophosphamide, cyclosporine or anti-thymocyte globulin.²¹³ Corticosteroids tend to be less effective in PRCA than in ITP or AIHA. In the very refractory cases, allogeneic HSCT 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.²¹³

Tumor Flare Reactions

Tumor flare reactions were commonly reported in patients with CLL treated with lenalidomide. In phase II studies of single-agent lenalidomide in relapsed/refractory CLL, tumor flare occurred in approximately 30% to 60% of patients.^{140,141} A higher incidence (approximately 50–90%) was reported in the first-line setting, although these reactions were limited to grade 1 or 2 events.^{88,90} Tumor flare reaction is typically observed as painful enlargement of lymph nodes, and may be accompanied by lymphocytosis, spleen enlargement, low-grade fever, rash, and/or bone pain. Tumor flare was more frequent among patients with enlarged (>5 cm) lymph nodes at baseline.¹⁴¹ For patients who experience tumor flare reactions while treated with lenalidomide-containing regimens, the panel recommends the use of steroids to manage lymph node enlargement and inflammation, and antihistamines to manage rash/pruritus. For patients with bulky (> 5 cm) lymph nodes prior to start of therapy, tumor flare prophylaxis with steroids may be considered for the first 10 to 14 days of therapy. Severe tumor flare reaction is generally rare if a CD20 monoclonal antibody is initiated at least 1 week prior to start of lenalidomide for those patients treated with the combination regimen.

Venous Thromboembolism

Lenalidomide was associated with increased risks for venous thromboembolism (deep vein thrombosis or pulmonary embolism) in patients with myelodysplastic syndromes or multiple myeloma, particularly when combined with dexamethasone or with chemotherapy agents.^{92,232-236} Published guidelines recommend that patients with multiple myeloma treated with lenalidomide- or thalidomide-containing combination regimens receive prophylactic anticoagulation with low-



molecular weight heparin or warfarin to prevent venous thromboembolism.²³⁴ Treatment with lenalidomide may also be associated with venous thromboembolic events in patients with CLL,^{140,141,237} but routine prophylactic anticoagulation is currently not indicated. Prophylaxis with daily low-dose aspirin (81 mg daily) may be considered in patients with extremely high platelet counts at baseline.

Tumor Lysis Syndrome

Patients with CLL and high white blood cell counts may occasionally experience tumor lysis syndrome and should be managed as outlined under “Tumor Lysis Syndrome” in the “Supportive Care” section of the Guidelines.

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