NCCN Guidelines® Insights

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2017

Featured Updates to the NCCN Guidelines

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Abstract

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are different manifestations of the same disease and managed in much the same way. The advent of novel CD20 monoclonal antibodies led to the development of effective chemoimmunotherapy regimens. More recently, small molecule inhibitors targeting kinases involved in a number of critical signaling pathways and a small molecule inhibitor of the BCL-2 family of proteins have demonstrated activity for the treatment of patients with CLL/SLL. These NCCN Guidelines Insights highlight important updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL for the treatment of patients with newly diagnosed or relapsed/refractory CLL/SLL.

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*Provided content development and/or authorship assistance.

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Release date: March 10, 2017; Expiration date: March 10, 2018

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for CLL/SLL
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for CLL/SLL

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^gSee Supportive Care for Patients with CLL/SLL (CSLL-C).

^hSee Rai and Binet Classification Systems (CSLL-B 1 of 2) and Lugano Modification of Ann Arbor Staging System (CSLL-B 2 of 2).

ⁱIncreased 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.

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

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

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

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

ⁿIn addition to the regimens listed in Diffuse Large B-Cell Lymphoma, R-HyperCVAD has also been used in this setting.

^oSalvi 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.

^pRe-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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CSLL-3

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) constitute approximately 7% of newly diagnosed non-Hodgkin’s lymphomas (NHL) cases.¹ In 2016, an estimated 18,960 people were diagnosed with CLL in the United States and an estimated 4,660 people died of the disease.² CLL/SLL is characterized by a progressive accumulation of leukemic cells in the blood, bone marrow, and lymphoid tissues.

CLL and SLL are different manifestations of the same disease and are managed in much the same way.³ The major difference between them is that a significant number of the abnormal lymphocytes are found in blood in CLL, in addition to bone marrow and lymphoid tissue; in SLL there are few, if any, abnormal lymphocytes circulating in the blood, and the bulk of disease is in the lymph nodes, bone marrow, and other lymphoid tissues.

During the past several decades, therapeutic options for CLL have evolved significantly. The advent

^gSee Supportive Care for Patients with CLL/SLL (CSLL-C).
^jAbsolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10⁹/L or symptoms related to leukostasis.
^kGiven incurability with conventional therapy, consider a clinical trial as first line of treatment.
^oSalvi 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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of immunomodulating agents (eg, lenalidomide) and CD20 (rituximab, obinutuzumab, and ofatumumab) and CD52 (alemtuzumab) monoclonal antibodies have led to the development of effective chemoimmunotherapy regimens. More recently, small molecule inhibitors targeting kinases involved in a number of critical signaling pathways (eg, Bruton tyrosine kinase [BTK], phosphatidylinositol 3-kinase [PI3K], and spleen tyrosine kinase) and a small molecule inhibitor of the BCL-2 family of proteins have shown promising activity in the treatment of patients with CLL (Tables 1 and 2).

These NCCN Guidelines Insights highlight important updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CLL/SLL for the treatment of patients with newly diagnosed or relapsed or refractory CLL/SLL.

First-Line Therapy

First-line therapy with fludarabine/cyclophosphamide/rituximab (FCR) results in high response rates

and improved overall survival (OS) in specific subgroups of fit patients with previously untreated CLL, especially those with mutated IGHV.^{4,5} In a phase II study of 300 patients with previously untreated CLL, at a median follow-up of 12.8 years, the overall response rate (ORR) was 95% (72% achieved a complete response [CR]),⁴ median progression-free survival (PFS) was 6.4 years, and the overall 12.8-year PFS rate was 30.9% (53.9% for those with mutated IGHV and 8.7% for unmutated IGHV). Minimal residual disease (MRD) negativity was achieved in 50.7% of patients with mutated IGHV, with a PFS rate of 79.8% at 12.8 years. In a multivariable analysis, unmutated IGHV and del(17p) by conventional karyotyping were significantly associated with inferior PFS. Long-term PFS was notable particularly for patients with mutated IGHV, with a plateau on the PFS curve beyond 10 years. In a large, international, randomized, phase III clinical trial (CLL8 study), 817 physically fit patients with previously untreated CLL (median age, 61 years) were randomized to receive

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CLL/SLL WITHOUT DEL(17p)/TP53 MUTATION

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

See monoclonal antibody and viral reactivation (CSLL-C)

FIRST-LINE THERAPY⁹RELAPSED/REFRACTORY THERAPY⁹

⁹See Supportive Care for Patients with CLL/SLL (CSLL-C).

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

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

^oSalvi 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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CSLL-5

up to 6 courses of either FCR (n=408) or fludarabine/cyclophosphamide (FC; n=409).⁵ The FCR regimen resulted in a higher ORR (90% vs 80%; $P<.001$) and CR rate (44% vs 22%; $P<.001$) compared with FC. With a median follow-up of 5.9 years, the median PFS was 56.8 months for FCR and 33 months for FC ($P<.001$); median OS was not reached for FCR and was 86.0 months for FC ($P=.001$).⁵ FCR was associated with a statistically significant survival benefit compared with FC in patients aged <65 years (5-year OS, 80.9% and 69.2%, respectively; $P=.002$); corresponding 5-year OS rates were 73.9% and 61.6%, respectively ($P=.288$). The incidence of prolonged neutropenia was significantly higher with the FCR regimen than with FC during the first year after treatment (16.6% vs 8.8%; $P=.007$).

Bendamustine, an alkylating agent with a low cross-resistance to other alkylating agents, was evaluated as first-line monotherapy and in combination with rituximab.⁶⁻⁸ In a multicenter phase II trial (CLL2M study), bendamustine/rituximab (BR) re-

sulted in high ORR rates (88%; CR, 23%) in previously untreated patients (n=117; 26% were aged >70 years), with similar response and survival outcomes among the subgroup of elderly patients (aged >70 years).⁶ After a median follow-up of 27 months, median PFS was 34 months and the OS rate was 90.5%. Thrombocytopenia (22%), neutropenia (20%), anemia (20%), allergic/infusion reactions (9%), and infections (8%) were the most common grade 3 or 4 toxicities.

The final analysis of the CLL10 study, which compared BR with FCR as first-line therapy for CLL in fit patients without del(17p) (n=567; Cumulative Illness Rating Scale [CIRS] score ≤6, creatinine clearance [CrCl] >70 mL/min), confirmed the superiority in PFS with FCR over BR in patients aged ≤65 years without significant comorbidities.⁷ The median age was 61.6 years for all patients, but a significantly higher proportion of patients were >65 years in the BR arm (39% vs 30%). After a median follow-up of 37.1 months, the ORR was 95% for FCR and 96%

CLL/SLL WITH DEL(17p)/TP53 MUTATION

⁹See Supportive Care for Patients with CLL/SLL (CSLL-C).

^jAbsolute lymphocyte count alone is not an indication for treatment unless above $200\text{--}300 \times 10^9/\text{L}$ or symptoms related to leukostasis.

^qCpG-stimulated karyotype is useful to identify high-risk patients, particularly for Bruton's tyrosine kinase (BTK) inhibitor therapy.

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

^sSee Response Criteria: CLL/SLL (CSLL-E).

^tFor patients with complex karyotype (≥ 3 abnormalities) in remission after BTK-inhibitor therapy, consider discussion of allogeneic transplant although data available do not support this as highly effective (Jagłowski et al. Br J Haematol 2012;159:82-87).

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CSLL-6

for BR ($P=1.0$) with no difference in OS (3-year OS rate, 91% vs 92%, respectively; $P=.89$). FCR resulted in a higher CR rate (40% vs 31%), more MRD negativity (59% vs 26% at 12 months; $P<.0001$; and 55% vs 27% at 18 months; $P=.002$), and longer median PFS (55.2 vs 41.7 months; $P=.0003$) compared with BR. The PFS benefit of FCR was significant in physically fit patients aged <65 years and in those with mutated *IGHV*; the median PFS was 53.6 and 38.5 months, respectively, for FCR and BR ($P=.0004$). There was no significant difference in PFS between FCR and BR for patients aged >65 years (median not reached vs 48.5 months, respectively; $P=.172$). Among patients with mutated *IGHV*, the median PFS was not reached for FCR compared with 55.4 months for BR ($P=.089$). The incidence of severe neutropenia and infections were significantly more frequent in the FCR arm (39% vs 25%), especially in those aged >65 years.

Updated results of the study confirmed that BR is also associated with a decreased risk of secondary

acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS).⁹ After a median follow-up of 58.2 months, the incidences of secondary AML and MDS were 3% and 1% in the FCR and BR arms, respectively. The results of the study confirm that FCR remains the standard first-line therapy for untreated CLL in fit patients and particularly for those with mutated *IGHV*. BR is an alternative treatment option for fit elderly patients or those with previous infections.

An ongoing phase III randomized trial is comparing rituximab/chlorambucil (R-chlorambucil) and BR as first- or second-line therapy in patients with CLL who are not candidates for fludarabine-based chemoimmunotherapy due to older age or presence of comorbid conditions.⁸ In an interim analysis (126 evaluable patients; 58 treated with BR, 68 treated with R-chlorambucil; median age, 74 years; range, 44–91), at the median follow-up of 24 months, the ORR among the patients who received first-line therapy was 91% in the BR group (CR,

CLL/SLL, Version 1.2017

SUGGESTED TREATMENT REGIMENS^{a,b}
(in order of preference)**CLL/SLL without del(17p)/TP53 mutation****First-line therapy****First-line therapy**

- Frail patient with significant comorbidity (not able to tolerate purine analogs)
 - ▶ Obinutuzumab + chlorambucil (category 1)
 - ▶ Ibrutinib^c (category 1)
 - ▶ Ofatumumab + chlorambucil
 - ▶ Rituximab + chlorambucil
 - ▶ Obinutuzumab (category 2B)
 - ▶ Rituximab (category 3)
 - ▶ Chlorambucil (category 3)

- Age ≥ 65 y and younger patients with significant comorbidities
 - ▶ Obinutuzumab + chlorambucil (category 1)
 - ▶ Ibrutinib^c (category 1)
 - ▶ Ofatumumab + chlorambucil
 - ▶ Rituximab + chlorambucil
 - ▶ Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated) $\pm$ rituximab^d
 - ▶ Obinutuzumab (category 2B)
 - ▶ Chlorambucil (category 3)
 - ▶ Rituximab (category 3)

First-line therapy

- Age < 65 y without significant comorbidities
 - ▶ Chemoimmunotherapy
 - ◊ FCR^e (fludarabine,^f cyclophosphamide, rituximab) (category 1)^d
 - ◊ FR^e (fludarabine,^f rituximab)^g
 - ◊ PCR (pentostatin, cyclophosphamide, rituximab)
 - ◊ Bendamustine $\pm$ rituximab^d
 - ▶ Ibrutinib^c

See Suggested Regimens for Relapsed/Refractory Therapy for CLL/SLL without del(17p)/TP53 mutation (2 of 5)

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

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

See Suggested Regimens for CLL/SLL with del(17p) (3 of 5)

^aSee references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.

^bSee Supportive Care for Patients with CLL/SLL (CSLL-C).

^cSee Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib) (CSLL-F).

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

^eAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those where a history of fludarabine-associated AIHA is suspected.

^fSee Discussion for further information on oral fludarabine.

^gNot for del(11q).

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CSLL-D
1 OF 5

24%) and 86% (CR, 9%) in the R-chlorambucil group.⁸ The median PFS was significantly longer in BR group than in the R-chlorambucil group (40 vs 30 months; $P=.003$), but the median OS was not significantly different (44 months vs not calculable). The incidence of adverse events (AEs) was similar between treatment groups (98% for BR vs 97% for R-chlorambucil), but the incidence of grade 3 AEs was higher for BR compared with R-chlorambucil (75% and 64%, respectively).

Obinutuzumab is a glycoengineered, humanized, type II antibody targeted against CD20. Results of the CLL11 study established obinutuzumab plus chlorambucil as the new standard of care for both elderly patients and those with comorbidities lacking del(17p).^{10,11} In this study, 781 patients with comorbid conditions (CIRS score > 6 , or estimated CrCl, 30–69 mL/min) were randomized to receive either chlorambucil (n=118), obinutuzumab plus chlorambucil (n=333), or rituximab plus chlorambucil (n=330).¹⁰ Combination obinutuzumab/chlorambucil and ritux-

imab/chlorambucil resulted in a significant improvement in median PFS compared with chlorambucil alone (26.7, 16.3, and 11.1 months, respectively; $P<.001$).¹⁰ The survival benefit was seen in all subgroups except patients with del(17p). After the median observation time of 39.0 months, obinutuzumab/chlorambucil significantly prolonged median PFS (28.7 vs 15.7 months; $P<.001$), and median time to next treatment (51 vs 38.2 months; $P<.0001$) compared with rituximab/chlorambucil. There was also a trend toward OS benefit for obinutuzumab.¹¹ The most frequent grade ≥ 3 toxicities with obinutuzumab/chlorambucil included neutropenia (35%), infusion-related reactions (21%), thrombocytopenia (11%), and infections (11%); neutropenia (28%) and infections (14%) were the most frequent grade ≥ 3 toxicities associated with rituximab/chlorambucil.

Ofatumumab (a fully human anti-CD20 monoclonal antibody) was evaluated in a multicenter, open-label, phase III study (COMPLEMENT 1) as first-line treatment for patients with untreated CLL

SUGGESTED TREATMENT REGIMENS^{a,b} (in order of preference)

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

Relapsed/Refractory Therapy

- Age <65 y without significant comorbidities
 - ▶ Ibrutinib^c (category 1)
 - ▶ Idelalisib + rituximab^{c,h} (category 1)
 - ▶ Idelalisib^c
 - ▶ Venetoclax^{i,j}
- Chemoimmunotherapy
 - ◊ FCR^{e,f}
 - ◊ FC + ofatumumab
 - ◊ PCR
 - ◊ Bendamustine ± rituximab
 - ◊ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
 - ◊ OFAR^g (oxaliplatin, fludarabine,^f cytarabine, rituximab)
 - ◊ Ibrutinib,^c bendamustine, rituximab (category 2B)
 - ◊ Idelalisib,^c bendamustine, rituximab (category 2B)
- Ofatumumab
- Obinutuzumab
- Lenalidomide^k ± rituximab
- Alemtuzumab^l ± rituximab
- HDMP + rituximab

^hIndicated 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.)

ⁱParticularly for patients deemed intolerant or refractory to ibrutinib or idelalisib.

^jSee Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).

^kLenalidomide 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.

^lWhile 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.

Second-line Extended Dosing

- Ofatumumab maintenance (for complete or partial response after relapsed or refractory therapy) (category 2B)

See Suggested Regimens for CLL/SLL with del(17p) (3 of 5)

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

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

Relapsed/Refractory Therapy

Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities

- ▶ Ibrutinib^c (category 1)
- ▶ Idelalisib + rituximab^{c,h} (category 1)
- ▶ Idelalisib^c
- ▶ Venetoclax^{i,j}
- Chemoimmunotherapy
 - ◊ Bendamustine ± rituximab
 - ◊ Reduced-dose FCR^{e,f}
 - ◊ Reduced-dose PCR
 - ◊ High-dose methylprednisolone (HDMP) + rituximab
 - ◊ Rituximab + chlorambucil
 - ◊ Ibrutinib,^c bendamustine, rituximab (category 3)
 - ◊ Idelalisib,^c bendamustine, rituximab (category 3)
- Ofatumumab
- Obinutuzumab
- Lenalidomide^k ± rituximab
- Alemtuzumab^l ± rituximab
- Dose-dense rituximab (category 2B)

^aSee references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.

^bSee Supportive Care for Patients with CLL/SLL (CSLL-C).

^cSee Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib) (CSLL-F).

^eAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those where a history of fludarabine-associated AIHA is suspected.

^fSee Discussion for further information on oral fludarabine.

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who were considered inappropriate for fludarabine-based regimens due to advanced age and/or comorbidities; 447 patients were randomized to ofatumumab/chlorambucil versus chlorambucil monotherapy.¹² After a median follow-up of 29 months, the median PFS was significantly longer for ofatumumab/chlorambucil compared with chlorambucil monotherapy (22.4 vs 13.1 months; $P < .001$)¹²; median OS was not reached in either arm. Ofatumumab/chlorambucil also resulted in a higher ORR (82% vs 69%; $P = .001$) and superior CR rate (12% vs 1%) compared with chlorambucil alone.

Ibrutinib, an irreversible inhibitor of BTK initially approved for relapsed or refractory CLL, was also evaluated in patients with untreated CLL/SLL, including those with del(17p).¹³⁻¹⁷ Five-year follow-up data from the multicenter phase Ib/II study, which included 31 patients aged ≥65 years with untreated CLL/SLL, confirmed that ibrutinib induces very durable responses across all subgroups, including those aged ≥65 years with

untreated CLL/SLL and those with del(17p), del(11q), or unmutated IGHV.¹⁴ After a median follow-up of 5 years, ibrutinib (420 mg) resulted in an ORR of 84% (CR, 29%); median PFS was not reached and the estimated PFS rate at 60 months was 92%. Responses were independent of the presence of high-risk features; however, the number of patients with del(17p), del(11q), trisomy 12, or elevated beta-2-microglobulin was small in this study. In another phase II trial that included 35 treatment-naïve patients with del(17p) treated with ibrutinib (aged ≥18 years; median, 62 years), at a median follow-up of 24 months, ibrutinib resulted in objective responses in 32 of 33 evaluable patients (55% experienced partial response [PR], and 42% experienced a PR with lymphocytosis) and the estimated OS at 24 months was 84%.¹⁵ The cumulative incidence of progression at 24 months was 9%. Grade ≥3 neutropenia, anemia, and thrombocytopenia were reported in 24%, 14%, and 10% of patients, respec-

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SUGGESTED TREATMENT REGIMENS^{a,b}
(in order of preference)

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

First-line Therapy

- Ibrutinib^c
- HDMP + rituximab
- Obinutuzumab + chlorambucil (category 3)
- Alemtuzumab^l ± rituximab

Relapsed/Refractory Therapy

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

Second-line Extended Dosing

- Ofatumumab maintenance (for complete or partial response after relapsed or refractory therapy) (category 2B)

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

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

See Suggested Regimens for CLL/SLL without del(17p) (1 of 5)

^aSee references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.^bSee Supportive Care for Patients with CLL/SLL (CSLL-C).^cSee Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib) (CSLL-F).^eAutoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those where a history of fludarabine-associated AIHA is suspected.^fSee Discussion for further information on oral fludarabine.^hIndicated 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.)^jSee Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).^kLenalidomide 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.^lWhile 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.^mThis is not effective in patients with lymph nodes >5 cm.

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CSLL-D
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tively; grade 3 pneumonia (6%) and rash (2%) were also reported.

The efficacy and safety of ibrutinib in patients aged ≥65 years with untreated CLL/SLL without del(17p) was demonstrated in a randomized phase III study (RESONATE-2; 269 patients were randomized to receive ibrutinib or chlorambucil as first-line therapy).¹⁶ After a median follow-up of 28.6 months, ibrutinib resulted in a significantly higher ORR (92% vs 36%; $P<.0001$) and significantly longer PFS (89% vs 34% at 24 months; $P<.0001$) compared with chlorambucil. With 41% of patients switching to ibrutinib, the estimated 2-year OS rates in the intent-to-treat population were 95% and 84% for patients treated with ibrutinib and chlorambucil, respectively.¹⁷ Ibrutinib was approved as first-line therapy for all patients, although the efficacy of ibrutinib as first-line therapy in patients aged <65 years without del(17p) has not been established in a randomized clinical trial.

Relapsed or Refractory Therapy

The current standards of care for relapsed or refractory CLL/SLL are ibrutinib, idelalisib, and idelalisib with rituximab and venetoclax for relapsed/refractory del(17p) CLL/SLL (see Table 2).

Ibrutinib has remarkable monotherapy activity with a favorable toxicity profile in patients with relapsed or refractory CLL.¹⁸⁻²⁰ In the phase III randomized RESONATE study, 391 patients with previously treated CLL were randomized to monotherapy with ibrutinib (420 mg/d) or ofatumumab.¹⁸ Most 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, the ibrutinib group experienced significantly prolonged PFS (median not reached vs 8.1 months for ofatumumab) and OS (HR for death in the ibrutinib group, 0.43; $P=.005$; 57% reduction in the risk of death). Among patients with del(17p), median PFS was not reached for ibrutinib compared with a median PFS of 5.8 months for ofatumumab.¹⁸

SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS (IBRUTINIB AND IDELALISIB)^{1,2,3}**IBRUTINIB**

- **Dosage**
 - ▶ **CLL:** The recommended dose of ibrutinib is 420 mg PO daily, continuous and should be continued until time of progression.
- **Lymphocytosis**
 - ▶ **CLL:** Upon initiation of ibrutinib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib therapy and may persist for several weeks on treatment.
- **Grade >2 bleeding events were observed in 6% of patients on ibrutinib; the mechanism is not well understood. Consider the benefit-risk of ibrutinib in patients requiring anti-platelet or anticoagulant therapies. Clinical trials excluded subjects on concurrent warfarin. Ibrutinib should be held 3 days before and after a minor surgical procedure and 7 days before and after a major surgical procedure. Ibrutinib should not be given concomitantly with warfarin.**
- **New-onset atrial fibrillation was reported in 6%–9%, associated with ibrutinib administration.²**
 - ▶ Consider non-warfarin anticoagulation
 - ▶ Monitor carefully
 - ▶ Consider switching to alternate therapy
 - ▶ Patients with recurrent atrial fibrillation that is not medically controllable should be changed to idelalisib.
- **Hypertension associated with ibrutinib has been uncommonly reported as a basis for discontinuation and should be managed with anti-hypertensives as appropriate. Ibrutinib should only be discontinued for uncontrollable hypertension.**
- **In CLL, at time of disease progression on ibrutinib, transition to next therapy as soon as possible upon stopping ibrutinib since progression may accelerate when ibrutinib is stopped. Treatment-free interval should be as short as possible.**

IDELALISIB

- **The recommended dose of idelalisib is 150 mg PO twice daily, per prescribing recommendations.**
- **Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.**
 - ▶ **Hepatotoxicity:** Monitor hepatic function prior to and during treatment. Interrupt if ALT/AST > 5 x ULN (upper limit of normal) and when resolved may resume at a reduced dose (100 mg PO twice daily).
 - ▶ **Diarrhea or colitis:** Monitor for the development of severe diarrhea or colitis. Interrupt until resolution and then reduce or discontinue idelalisib. Severe diarrhea and colitis can be managed with systemic or nonabsorbable steroids.
 - ▶ **Pneumonitis:** Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Discontinue idelalisib.
 - ▶ **Intestinal perforation:** Discontinue idelalisib if intestinal perforation is suspected.
- **Lymphocytosis**
 - ▶ **CLL:** Upon initiation of idelalisib, transient increase in absolute lymphocyte count is expected in most patients, which does not signify disease progression. This onset of isolated lymphocytosis occurs during the first few weeks of idelalisib therapy and may persist for several weeks on treatment.
- **CMV: Monitor per institutional guidelines or consult with Infectious Disease.**

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

2. Ibrutinib package insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205552s001lbl.pdf.

3. Idelalisib package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205858lbl.pdf.

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At 12 months, the OS rate was 91% and 81%, respectively, for ibrutinib and ofatumumab; the ORR was also significantly higher with ibrutinib (42% vs 4%; $P < .001$). The most frequent nonhematologic AEs were mild (grades 1/2) with diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group, and fatigue, infusion-related reactions, and cough in the ofatumumab group. Updated results of this study also confirmed that ibrutinib significantly improved ORR, PFS, and OS compared with ofatumumab in patients with CLL/SLL who had received ≥ 1 prior treatment.¹⁹ With a median follow-up of 16 months, the ORR (90% vs 25%; $P < .0001$), median PFS (not reached vs 8.1 months for ofatumumab; $P < .0001$), and OS rates (18-month OS, 85% and 78%, respectively) were significantly improved for ibrutinib. Results of the phase II RESONATE-17 study further confirmed the safety and efficacy of ibrutinib in 144 patients with relapsed or refractory CLL with del(17p).²⁰ In an extended analysis with a median follow-up of 27.6 months, the investigator-assessed

ORR and 24-month PFS and OS rates were 83%, 63%, and 75%, respectively.²⁰

Idelalisib (the isoform-selective oral inhibitor of PI3K- δ) has demonstrated promising clinical activity in phase I–II studies in patients with relapsed or refractory CLL/SLL, both as monotherapy and in combination with rituximab.^{21–23} In the multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with either idelalisib (150 mg) or placebo.²¹ Most of the patients (78%) were aged ≥ 65 years, 40% had moderate renal dysfunction (CrCl, < 60 mL/min), 35% had poor bone marrow function (grade ≥ 3 cytopenias), and 85% had a CIRS score > 6 . At the first planned interim analysis, the study was stopped early because of the overwhelming efficacy of idelalisib plus rituximab.²¹ At 24 weeks, the PFS rate was 93% and 46% in the idelalisib and placebo groups, respectively. Among patients with relapsed CLL with coexisting conditions, combination idelalisib/rituximab significantly improved ORR (81% vs 13%;

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SPECIAL CONSIDERATIONS FOR THE USE OF SMALL-MOLECULE INHIBITORS (IBRUTINIB AND IDELALISIB)^{1,2,3}**Co-administration with CYP3A Inhibitors and Inducers^{2,3}**

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

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

2. Ibrutinib package insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205552s001lbl.pdf.

3. Idelalisib package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205858lbl.pdf.

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$P < .001$), PFS (not reached in the idelalisib group vs 5.5 months for placebo), and OS at 12 months (92% vs 80%; $P = .02$) compared with rituximab plus placebo. Grade 3 or 4 AEs (pneumonia, pyrexia, and febrile neutropenia) were reported in 40% of patients in the idelalisib group and 35% in the placebo group. The second interim analysis of this study also confirmed the superior safety and efficacy of idelalisib plus rituximab in terms of ORR, PFS, and OS.²⁴ The combination 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).²² A post hoc analysis of 39 patients with relapsed or refractory SLL enrolled in phase I ($n = 11$) and II ($n = 28$) studies (that evaluated the efficacy and safety of patients on idelalisib with relapsed or refractory indolent NHL) showed that idelalisib monotherapy has substantial clinical activity in the subset of patients with relapsed or refractory SLL²³: the ORR was 55% (6 of 11) and 61% (17 of 28); median duration of response was 2.3

and 12.5 months; and median PFS was 3.7 and 11.4 months, respectively. Idelalisib monotherapy is approved for the treatment of relapsed SLL in patients who have received ≥ 2 prior systemic therapies.

Idelalisib in combination with rituximab is approved for the treatment of relapsed CLL in patients for whom rituximab monotherapy would be considered appropriate due to other comorbidities (reduced renal function as measured by CrCl <60 mL/min, or NCI CTCAE grade ≥ 3 neutropenia or thrombocytopenia resulting from myelotoxic effects of prior treatment with cytotoxic agents). Due to infection-related toxicity and deaths seen in phase III clinical trials with idelalisib in previously untreated CLL, it should not be used in the first line. Prescribers should be aware of this increased risk for infections in patients with relapsed or refractory CLL. Infection prophylaxis for herpes simplex virus, *Pneumocystis jirovecii* pneumonia (PJP), and routine monitoring for cytomegalovirus (CMV) reactivation are recommended for patients on idelalisib.

VENETOCLAX: RECOMMENDED TLS PROPHYLAXIS AND MONITORING BASED ON TUMOR BURDEN^a

- Initiate venetoclax at 20-mg dose for one week and gradual step wise ramp-up over 5 weeks to target dose of 400 mg daily
- Consider all patient comorbidities before final determination of prophylaxis and monitoring schedule

Tumor Burden ^b	Prophylaxis ^c	Blood Chemistry Monitoring ^{e,f}
Low All lymph nodes <5 cm AND Absolute lymphocyte count (ALC) <25 x10 ⁹ /L	<ul style="list-style-type: none"> • Oral hydration (1.5–2 L) • Allopurinol^d 	Outpatient <ul style="list-style-type: none"> • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses
Medium Any lymph node 5 cm to <10 cm OR ALC ≥25 x10 ⁹ /L	<ul style="list-style-type: none"> • Oral hydration (1.5–2 L) and consider additional intravenous hydration • Allopurinol 	Outpatient <ul style="list-style-type: none"> • Pre-dose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp-up doses • Consider hospitalization for patients with CrCl <80 mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High Any lymph node ≥10 cm OR ALC ≥25 x10 ⁹ /L AND any lymph node ≥5 cm	<ul style="list-style-type: none"> • Oral hydration (1.5–2 L) and intravenous hydration (150–200 mL/h as tolerated) • Allopurinol • Consider rasburicase if baseline uric acid is elevated 	In hospital at first dose of 20 mg and 50 mg <ul style="list-style-type: none"> • Pre-dose, 4, 8, 12, and 24 hours Outpatient at subsequent ramp-up doses <ul style="list-style-type: none"> • Pre-dose, 6 to 8 hours, 24 hours

^aPrescribing information for venetoclax. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf

^bLymph node size should be evaluated by CT scan.

^cAdminister intravenous hydration for any patient who cannot tolerate oral hydration.

^dStart allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.

^eEvaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.

^fFor patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

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CSLL-G

Venetoclax, a small-molecule BCL2 inhibitor that induces CLL cell apoptosis, has demonstrated activity in relapsed or refractory CLL.^{25,26} In a phase II study of 107 patients (61 patients aged ≥65 years; 46 patients aged <65 years) with relapsed or refractory del(17p) CLL, at a median follow-up of 12.1 months, venetoclax resulted in an ORR of 79.4% as assessed by the independent review committee.²⁵ Venetoclax resulted in a high ORR (>70%) in all subgroups of patients with additional risk features [eg, fludarabine-refractory status, bulky disease, del(17p), TP53 mutation]; estimated 12-month PFS and OS rates were 72% and 86.7%, respectively. Neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%) were the most common treatment-related AEs. Venetoclax has also shown promising activity in patients with relapsed or refractory CLL who have failed to respond or are intolerant to ibrutinib or idelalisib.²⁶ In a phase II study of 64 patients with relapsed or refractory CLL after prior treatment with ibrutinib (arm A; n=43; 39 patients

refractory to ibrutinib) or idelalisib (arm B; n=21; 14 patients refractory to idelalisib), venetoclax resulted in an ORR of 70% (arm A) and 48% (arm B).²⁶ In the subset of patients with CLL refractory to ibrutinib or idelalisib, the ORR was 67% (26 of 39, arm A) and 57% (8 of 14, arm B), respectively. The estimated 12-month PFS and OS rates for all patients were 72% and 90%, respectively; median PFS and OS was not reached at the time of analysis. Neutropenia can be a longer-term toxicity requiring growth factor support and/or venetoclax dose adjustment. Initiation at a lower dose (20 mg for 1 week) and a gradual stepwise ramp-up over 5 weeks to the target dose (400 mg/d) along with prophylaxis for tumor lysis syndrome (TLS) is recommended to mitigate the risk and frequency of TLS in patients receiving venetoclax (see CSLL-G; page 304).^{25,27}

Ofatumumab is approved for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. However, it has demonstrated activity in patients with CLL refractory to fludarabine and

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Table 1. Treatment Options for First-line Therapy

Trial	Regimen	N	Median Age	Median Follow-up	ORR	CR	PFS	OS
CLL8 ⁵	FCR	408	61 y; ≥65 y (31%)	5.9 y	90%	44%	46.8% at 5 y	78.7% at 5 y
	FC	409	61 y; ≥65 y (29%)		80%	22%	25.5% at 5 y	66.9% at 5 y
CLL10 ⁷	FCR	282	61.6 y; ≥65 y (30%)	37.1 mo	95%	40%	55.2 mo	91% at 3 y
	BR	279	61.6 y; ≥65 y (39%)		96%	31%	41.7 mo	92% at 3 y
CLL11 ^{10,11}	Obinutuzumab + chlorambucil	333	73 y	39.0 mo	78%	21%	28.7 mo	Not reached
	Rituximab + chlorambucil	330			65%	7%	15.7 mo	Not reached
CLL11 ^{10,11}	Obinutuzumab + chlorambucil	238	73 y	42.4 mo	77%	22%	31.1 mo	Not reached
	Chlorambucil	118			31% (PR)	N/A	11.1 mo	58.5 mo
COMPLEMENT 1 ¹²	FC + ofatumumab	226	69 y	29 mo	82%	12%	22.4 mo	Not reached
	Chlorambucil	221			69%	1%	13.1 mo	Not reached
RESONATE-2 ¹⁷	Ibrutinib	136	73 y ≥70 y (71%)	28.6 mo	92%	18%	89% at 2 y	95% at 2 y
	Chlorambucil	133	72 y ≥70 y (70%)		36%	N/A	34% at 2 y	84% at 2 y
PCYC-1102 ¹⁴	Ibrutinib	31	68 y ≥70 y (43%)	5 y	84%	29%	92% at 5 y	

Abbreviations: BR, bendamustine/rituximab; CR, complete response; FC, fludarabine/cyclophosphamide; FCR, fludarabine/cyclophosphamide/rituximab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

alemtuzumab or in patients for whom alemtuzumab is contraindicated due to bulky lymphadenopathy.^{28,29} The COMPLEMENT 2 study evaluated FC plus ofatumumab versus FC alone in patients with relapsed CLL (n=365).³⁰ FC plus ofatumumab was associated with improved PFS and a manageable safety profile. Median PFS (primary end point; assessed by the independent review committee) was 28.9 and 18.8 months, respectively, for FC plus ofatumumab versus FC ($P=.0032$); no significant difference in OS was seen between the treatment arms. The incidences of grade ≥3 AEs were 74% and 69%, respectively, for the 2 treatment groups. Neutropenia was the most common AE reported in 49% of pa-

tients treated with FC plus ofatumumab and in 36% treated with FC.

The phase III randomized trial PROLONG evaluated the efficacy and safety of ofatumumab maintenance versus observation in 474 patients with relapsed CLL in CR or PR after second-line or third-line therapy.³¹ At a median follow-up of 19.1 months, ofatumumab maintenance resulted in improved PFS (29.4 vs 15.2 months, respectively; $P<.0001$). Neutropenia (24%) and infections (13%) were the most common grade ≥3 AEs associated with ofatumumab maintenance. Ofatumumab maintenance is approved for patients with recurrent or pro-

Table 2. Treatment Options for Relapsed/Refractory Therapy

Trial	Regimen	N	Median Age	Median Follow-up	ORR	PFS	OS
RESONATE ¹⁹							
	Ibrutinib	195	67 y	16 mo	90%	Not reached	85% at 18 mo
	Ofatumumab	196	≥70 y (40%)		25%	8.1 mo	78% at 18 mo
RESONATE-17 ²⁰							
	Ibrutinib	144	64 y	27.6 mo	83%	63% at 24 mo	75% at 24 mo
PCYC-1102 ¹⁴							
	Ibrutinib	101	68 y ≥70 y (43%)	5 y	86%	43% at 5 y	
Furman et al ²¹							
	Idelalisib + rituximab	110	71 y	24 wk	81%	93% at 24 wk	92% at 12 mo
	Chlorambucil	110	≥65 y (78%)		13%	46% at 24 wk	80% at 12 mo
Stilgenbauer et al ²⁵							
	Venetoclax	107	67 y ≥65 y (57%)	12.1 mo	79.4%	72% at 12 mo	86.7% at 12 mo

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

gressive CLL who are in CR or PR after ≥2 lines of prior treatment.

Assessment of Functional Status and Comorbidity

CLL/SLL is diagnosed mainly in older adults, with a median age at diagnosis of 72 years; approximately 70% of patients are diagnosed at age ≥65 years and 40% at age ≥75 years.³² Comorbidities are frequently present in older patients. In addition, organ function and bone marrow reserve decline with increasing age. CIRS, Charlson comorbidity index, and NCI comorbidity index are some of the scoring systems that can be used to assess comorbidities in patients with CLL. CIRS in combination with CrCl was used by the German CLL Study Group (GCLLSG) to assess the overall fitness of patients enrolled in clinical trials.^{33,34} In a study that assessed the comorbidity burden and investigated its impact on treatment in 555 patients with untreated CLL enrolled in 2 GCLLSG trials, 26% of patients had comorbidities involving the metabolic/endocrine system, 21% had comorbidities in vascular system, and 12% had cardiac comorbidities.³³ The presence of multiple comorbidities (≥2 comorbidities) was an independent predictor of clinical outcome independent of patients' age or disease stage.³³ The median OS (71.7 vs 90.2 months; $P<.001$) and PFS (21.0 vs 31.5 months; $P<.01$) were

significantly shorter for patients with ≥2 comorbidities than for those with <2 comorbidities. These findings underscore the need to assess comorbidities, in addition to patient age and performance status (PS), before treatment selection. Older patients with adequate functional status can be treated with more active or intensive therapies,³⁵ and should be evaluated for cytogenetic abnormalities using fluorescence in situ hybridization. Patient age and the presence or absence of del(17p) or *TP53* mutations should then help direct treatment options, as discussed in the following section.

Treatment Recommendations

Early-stage disease in some patients may have an indolent course and in others may progress rapidly to advanced disease requiring immediate treatment. Patients with stage II–IV SLL, low-risk CLL (Rai stage 0; Binet A), or intermediate-risk CLL (Rai stage I–II; Binet B) may benefit from treatment if they become symptomatic or show evidence of progressive disease.³⁶ Patients with advanced-stage or high-risk CLL (Rai stage III–IV; Binet C) with progressive cytopenia require treatment (see CSLL-3; page 295). Selected patients with mild, stable cytopenia may continue to be observed.

Absolute lymphocyte count alone is not an indication for treatment unless it is >200 to $300 \times 10^9/L$.

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or symptoms related to leukostasis occur.³⁶ Indications for initiating treatment include severe fatigue, weight loss, night sweats, and fever without infection; threatened end-organ function; progressive bulky disease (enlarged spleen or lymph nodes); progressive anemia or thrombocytopenia; or autoimmune anemia/thrombocytopenia unresponsive to corticosteroids.³⁶ Asymptomatic patients should be observed until these indications become apparent. Recommendations for patients with indications for treatment are based on patient's age or functional status (comorbidity index/PS), as well as the presence or absence of del(17p) or TP53 mutations.

The age cutoff of 65 years is used in most clinical trials, including those conducted by the GCLLSG. In a retrospective analysis that evaluated the impact of age on outcome after initial treatment with different chemoimmunotherapy and chemotherapy regimens in patients with CLL enrolled in CALGB trials, the benefit of fludarabine compared with chlorambucil decreased marginally with age, with estimated hazard ratios of 0.70, 0.76, and 0.81 at 65, 70, and 75 years, respectively.³⁷ The benefit of fludarabine relative to chlorambucil also decreased at an earlier age for OS than for PFS, with the estimated hazard ratios of 0.88, 1.01, and 1.15 at 65, 70, and 75 years, respectively. In addition, approximately 44% of patients aged >65 years have some degree of chronic kidney disease, which also increases the likelihood of toxicity associated with fludarabine-based regimens.³⁸ Based on these data, the panel decided to change the age cutoff from 70 to 65 years.

CLL Without del(17p) or TP53 Mutations

First-Line Therapy: Obinutuzumab/chlorambucil (category 1),^{10,11} ibrutinib (category 1),¹⁶ and ofatumumab/chlorambucil¹² are the preferred treatment options for frail patients with significant comorbidities (eg, not able to tolerate purine analogs) or patients aged ≥65 years and younger patients with significant comorbidities (see CSLL-5; page 297). Bendamustine with or without rituximab is a reasonable alternative for patients aged ≥65 years who are otherwise eligible for chemoimmunotherapy.^{6,7} In the CLL11 trial, there was a clinically meaningful improvement in PFS with a trend toward improved OS in patients treated with obinutuzumab/chlorambucil versus rituximab/chlorambucil.^{10,11} Therefore,

rituximab/chlorambucil should be reserved for patients who cannot tolerate obinutuzumab.^{39,40}

With multiple randomized studies showing a survival advantage for combination regimens containing chlorambucil or rituximab compared with monotherapy with either of these agents,^{10,12} most of the panel members acknowledged that monotherapy with chlorambucil or rituximab is not an effective first-line treatment even for frail patients with comorbid conditions. However, some panel members felt that given the favorable tolerability profile, monotherapy with rituximab or chlorambucil may be an appropriate treatment option for a small fraction of very frail patients or patients aged ≥65 years with substantial comorbidities or decreased PS for whom more intensive regimens are not appropriate.^{41,42} Rituximab and chlorambucil are included as alternate treatment options (category 3).

In patients aged <65 years without significant comorbidities, fludarabine-based chemoimmunotherapy has emerged as the standard of care, especially in those with mutated IGHV.^{4,5} Therefore, chemoimmunotherapy with FCR is the preferred treatment option (category 1) for these patients. FR, pentostatin/cyclophosphamide/rituximab (PCR), or bendamustine with or without rituximab are included as alternate options for chemoimmunotherapy.

The panel acknowledged that there are no data to support the inclusion of ibrutinib as a category 1 recommendation for patients aged <65 years, because the RESONATE-2 trial (on which the FDA based its approval of ibrutinib for first-line therapy in all patients with CLL/SLL) established the efficacy of ibrutinib as first-line therapy only in patients aged ≥65 years without del(17p).¹⁶ However, with the recent FDA approval, some panel members agreed that ibrutinib may be an appropriate option instead of chemoimmunotherapy in younger patients with unmutated IGHV who do want to enroll in a clinical trial. Therefore, the panel included ibrutinib as a category 2A recommendation for first-line therapy for patients aged <65 years without del(17p).

Relapsed or Refractory Therapy: Ibrutinib (category 1),^{18,19} idelalisib/rituximab (category 1),²¹ idelalisib,²³ and venetoclax (particularly for patients deemed intolerant or refractory to ibrutinib or idelalisib)²⁶ are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities. The results of recent phase

III trials have shown that the addition of idelalisib or ibrutinib to BR significantly improves PFS in patients with relapsed or refractory CLL.^{43,44} BR with idelalisib or ibrutinib is included as an alternate option regardless of patient age and comorbidities.

For frail patients with significant comorbidities or patients aged ≥ 65 years and younger patients with comorbidities, reduced-dose FCR or PCR, bendamustine with or without rituximab, high-dose methylprednisolone (HDMP) or chlorambucil with rituximab, monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or dose-dense rituximab are included as alternative options. For patients aged < 65 years without significant comorbidities, chemoimmunotherapy (FCR, FC + ofatumumab, PCR, bendamustine $\pm$ rituximab, CHOP + rituximab, OFAR [oxaliplatin/fludarabine/cytarabine/rituximab]), monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or HDMP with rituximab are included as alternate options.

Ofatumumab maintenance (category 2B) is recommended for patients who are in CR or PR as second-line therapy.³¹ Allogeneic hematopoietic cell transplant (HCT) can be considered for select patients (without significant comorbidities) after reinduction of remission.

CLL With del(17p) or TP53 Mutations

Enrollment in an appropriate clinical trial is recommended for patients with del(17p). In the absence of appropriate clinical trials, ibrutinib is the preferred treatment option for first-line therapy^{13,15}; HDMP plus rituximab,^{45,46} obinutuzumab/chlorambucil,¹⁰ and alemtuzumab with or without rituximab⁴⁷⁻⁴⁹ are included as alternate treatment options (see CSLL-D, 3 of 5; page 301). The efficacy of ibrutinib in del(17p) CLL/SLL exceeds the results of alternative regimens in the upfront and salvage settings, and should be considered the best choice in the absence of a contraindication.

Recent reports suggest that complex karyotype (≥ 3 unrelated chromosomal abnormalities in > 1 cell on CpG-stimulated karyotype of CLL cells) is a stronger predictor of poor clinical outcomes than del(17p) in patients with relapsed or refractory CLL treated with ibrutinib-based regimens.^{50,51} In an analysis of 88 patients with relapsed or refractory CLL

treated with ibrutinib-based regimens, in a multivariate analysis, only complex karyotype was significantly associated with inferior event-free survival ($P = .006$), whereas complex karyotype ($P = .008$) and fludarabine-refractory CLL ($P = .005$) were independently associated with inferior OS.⁵¹ Complex karyotype has also been identified as an independent prognostic factor for shorter time to first treatment.⁵² CpG-stimulated karyotyping is useful for identifying high-risk patients, particularly for treatment with ibrutinib.

Patients with response to first-line therapy should be considered for allogeneic HCT, if complex karyotype is present. However, available data suggest that complex karyotype (≥ 5 abnormalities) is associated with inferior OS and event-free survival after allogeneic SCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics.⁵³ Allogeneic HCT is not recommended for patients with del(17p) CLL/SLL responding to first-line therapy with ibrutinib, if complex karyotype is not present. Ofatumumab maintenance (category 2B) is recommended for patients experiencing CR or PR to second-line therapy.³¹

Patients with no response to first-line therapy should be enrolled in clinical trials or be treated with second-line therapy for relapsed or refractory disease; preferred options for relapsed or refractory disease are ibrutinib,¹⁸⁻²⁰ venetoclax,²⁵ idelalisib/rituximab,²² and idelalisib.²³

Special Considerations for the Use of Small Molecule Inhibitors

Ibrutinib and idelalisib cause early mobilization of lymphocytes into the blood, resulting in a transient increase in absolute lymphocyte count in most patients, which does not signify disease progression.^{54,55} This onset of isolated lymphocytosis occurs during the first few weeks of ibrutinib treatment and may persist for several weeks on treatment. Although lymphocytosis can sometimes be profound, clinical consequence (ie, leukostasis) is extremely rare and treatment should be continued. Slow or incomplete resolution of lymphocytosis does not appear to impact outcome as measured by PFS (CSLL-F; pages 302 and 303).⁵⁴

Atrial fibrillation (grade ≥ 3) and major hemorrhage (defined as serious or grade ≥ 3 bleeding events or central nervous system hemorrhage of any grade)

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have been reported in 6% and 4% of patients treated with ibrutinib, respectively.^{13,16} The benefit and risk of ibrutinib should be evaluated in patients requiring antiplatelet or anticoagulant therapies. Patients requiring warfarin have been excluded from clinical trials evaluating ibrutinib, and should not be given concomitantly with warfarin. Hypertension (grade ≥ 3) associated with ibrutinib (reported in 20%) has uncommonly been the basis for discontinuation and should be managed with antihypertensives as appropriate.¹³ Alternate treatment should be considered, especially in patients with hypertension that is not medically controllable. At the time of disease progression on ibrutinib, transition to alternate treatment should be performed as soon as possible upon stopping ibrutinib, because progression may accelerate when ibrutinib is stopped. Treatment-free interval should be as short as possible (CSLL-F; pages 302 and 303).

Fatal and/or serious hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation have been observed in patients treated with idelalisib.⁵⁶ Hepatotoxicity is a major concern in younger patients treated with idelalisib as first-line therapy.⁵⁷ Close monitoring of transaminase levels is essential, and concurrent administration of idelalisib

with other hepatotoxic drugs should be avoided. Idelalisib is also associated with opportunistic infections and febrile neutropenia. PJP and CMV reactivation have been reported in patients treated with idelalisib, and the risk of developing these opportunistic infections is highest in the first 6 months of treatment.⁴³ The addition of CD20 monoclonal antibody or chemoimmunotherapy to idelalisib increases the risk of febrile neutropenia. Appropriate anti-infective prophylaxis and routine monitoring for early signs of infectious complications and CMV reactivation is recommended for patients receiving idelalisib (CSLL-F; pages 302 and 303).

Conclusions

The choice of first-line treatment for CLL/SLL should be based on disease stage, presence or absence of del(17p) or TP53. Ibrutinib, idelalisib ($\pm$ rituximab), and venetoclax are effective treatment options for relapsed or refractory del(17p) CLL/SLL. Careful monitoring of AEs after treatment initiation and supportive care for treatment-related complications should be an integral part of management of patients with CLL/SLL.

References

1. A clinical evaluation of the international lymphoma study group classification of non-Hodgkin's lymphoma. The non-Hodgkin's lymphoma classification project. *Blood* 1997;89:3909–3918.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7–30.
3. Tsimberidou AM, Wen S, O'Brien S, et al. Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. *J Clin Oncol* 2007;25:4648–4656.
4. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood* 2015;127:303–309.
5. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood* 2016;127:208–215.
6. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol* 2012;30:3209–3216.
7. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol* 2016;17:928–942.
8. Michallet AS, Aktan M, Schuh A. Rituximab in combination with bendamustine or chlorambucil for the treatment of chronic lymphocytic leukemia: primary results from the randomized phase IIIb MaLe study. Abstract 178. Available at: https://static1.squarespace.com/static/52f8f139e4b0bae912c96d0d/t/562a508ae4b05e1ace338235/1445613706834/IIWCLL+Report+_v4+.pdf. Accessed February 13, 2017.
9. Eichhorst BF, Bahlo J, Maurer C, et al. Favorable toxicity profile and long term outcome of elderly, but physically fit CLL patients (pts) receiving first line bendamustine and rituximab (BR) frontline chemoimmunotherapy in comparison to fludarabine, cyclophosphamide, and rituximab (FCR) in advanced chronic lymphocytic leukemia (CLL): update analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 study) [abstract]. *Blood* 2016;128:Abstract 4382.
10. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014;370:1101–1111.
11. Goede V, Fischer K, Bosch F, et al. Updated survival analysis from the CLL11 study: obinutuzumab versus rituximab in chemoimmunotherapy-treated patients with chronic lymphocytic leukemia [abstract]. *Blood* 2015;126:Abstract 1733.
12. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet* 2015;385:1873–1883.
13. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood* 2015;125:2497–2506.
14. O'Brien SM, Furman RR, Coutre SE, et al. Five-year experience with single-agent ibrutinib in patients with previously untreated and relapsed/refractory chronic lymphocytic leukemia/small lymphocytic leukemia [abstract]. *Blood* 2016;128:Abstract 233.
15. Farooqui MZ, Valdez J, Martyn S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. *Lancet Oncol* 2015;16:169–176.
16. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med* 2015;373:2425–2437.
17. Barr P, Robak T, Owen CJ, et al. Updated efficacy and safety from the phase 3 RESONATE-2 study: ibrutinib as first-line treatment option in patients

- 65 years and older with chronic lymphocytic leukemia/small lymphocytic leukemia [abstract]. *Blood* 2016;128:Abstract 234.
18. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014;371:213–223.
 19. Brown JR, Hillmen P, O'Brien S, et al. Updated efficacy including genetic and clinical subgroup analysis and overall safety in the phase 3 RESONATE trial of ibrutinib versus ofatumumab in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma [abstract]. *Blood* 2014;124:Abstract 3331.
 20. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. *Lancet Oncol* 2016;17:1409–1418.
 21. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2014;370:997–1007.
 22. Sharman JP, Coutre SE, Furman RR, et al. Efficacy of idelalisib in CLL subpopulations harboring del(17p) and other adverse prognostic factors: results from a phase 3, randomized, double-blind, placebo-controlled trial [abstract]. *J Clin Oncol* 2014;32(15 Suppl):Abstract 7011.
 23. Gopal AK, Davies AJ, Flinn IW, et al. Idelalisib monotherapy and durable responses in patients with relapsed or refractory small lymphocytic lymphoma (SLL) [abstract]. *Blood* 2015;126:Abstract 2743.
 24. Sharman JP, Coutre SE, Furman RR, et al. Second interim analysis of a phase 3 study of idelalisib (Zydelig) plus rituximab (R) for relapsed chronic lymphocytic leukemia (CLL): efficacy analysis in patient subpopulations with del(17p) and other adverse prognostic factors [abstract]. *Blood* 2014;124:Abstract 330.
 25. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2016;17:768–778.
 26. Jones J, Choi MY, Mato AR, et al. Venetoclax (VEN) monotherapy for patients with chronic lymphocytic leukemia (CLL) who relapsed after or were refractory to ibrutinib or idelalisib [abstract]. *Blood* 2016;128:Abstract 637.
 27. Seymour JF. Effective mitigation of tumor lysis syndrome with gradual venetoclax dose ramp, prophylaxis, and monitoring in patients with chronic lymphocytic leukemia. *Ann Hematol* 2016;95:1361–1362.
 28. Wierda WG, Padmanabhan S, Chan GW, et al. Ofatumumab is active in patients with fludarabine-refractory CLL irrespective of prior rituximab: results from the phase II international study. *Blood* 2011;118:5126–5129.
 29. Osterborg A, Jewell RC, Padmanabhan-Iyer S, et al. Ofatumumab monotherapy in fludarabine-refractory chronic lymphocytic leukemia: final results from a pivotal study. *Haematologica* 2015;100:e311–314.
 30. Robak T, Warzocha K, Govind Babu K, et al. Ofatumumab plus fludarabine and cyclophosphamide in relapsed chronic lymphocytic leukemia: results from the COMPLEMENT 2 trial. *Leuk Lymphoma* 2017;58:1084–1093.
 31. van Oers MH, Kuliczowski K, Smolej L, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. *Lancet Oncol* 2015;16:1370–1379.
 32. SEER Stat Facts: Chronic Lymphocytic Leukemia (CLL). National Cancer Institute Web site. Available at: <http://seer.cancer.gov/statfacts/html/clyl.html>. Accessed August 2012.
 33. Goede V, Cramer P, Busch R, et al. Interactions between comorbidity and treatment of chronic lymphocytic leukemia: results of German Chronic Lymphocytic Leukemia Study Group trials. *Haematologica* 2014;99:1095–1100.
 34. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *J Am Geriatr Soc* 2008;56:1926–1931.
 35. Satram-Hoang S, Reyes C, Hoang KQ, et al. Treatment practice in the elderly patient with chronic lymphocytic leukemia-analysis of the combined seer and medicare database. *Ann Hematol* 2014;93:1335–1344.
 36. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008;111:5446–5456.
 37. Woyach JA, Ruppert AS, Rai K, et al. Impact of age on outcomes after initial therapy with chemotherapy and different chemoimmunotherapy regimens in patients with chronic lymphocytic leukemia: results of sequential cancer and leukemia group b studies. *J Clin Oncol* 2013;31:440–447.
 38. Stevens LA, Li S, Wang C, et al. Prevalence of CKD and comorbid illness in elderly patients in the United States: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2010;55:S23–33.
 39. 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.
 40. Foa R, Giudice ID, Cuneo A, et al. Chlorambucil plus rituximab with or without maintenance rituximab as first-line treatment for elderly chronic lymphocytic leukemia patients. *Am J Hematol* 2014;89:480–486.
 41. Hainsworth JD, Litchy S, Barton JH, et al. Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2003;21:1746–1751.
 42. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood* 2009;114:3382–3391.
 43. Zelenetz AD, Brown JR, Delgado J, et al. Updated analysis of overall survival in randomized phase III study of idelalisib in combination with bendamustine and rituximab in patients with relapsed/refractory CLL [abstract]. *Blood* 2016;128:Abstract 231.
 44. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (helios): a randomised, double-blind, phase 3 study. *Lancet Oncol* 2016;17:200–211.
 45. Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. *Leuk Lymphoma* 2007;48:2412–2417.
 46. Castro JE, Sandoval-Sus JD, Bole J, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. *Leukemia* 2008;22:2048–2053.
 47. Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood* 2002;99:3554–3561.
 48. Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. *Blood* 2004;103:3278–3281.
 49. Fiegl M, Stauder R, Steurer M, et al. Alemtuzumab in chronic lymphocytic leukemia: final results of a large observational multicenter study in mostly pretreated patients. *Ann Hematol* 2014;93:267–277.
 50. Woyach JA, Ruppert AS, Lozanski G, et al. Association of disease progression on ibrutinib therapy with the acquisition of resistance mutations: a single-center experience of 267 patients [abstract]. *J Clin Oncol* 2014;32(Suppl):Abstract 7010.
 51. Thompson PA, O'Brien SM, Wierda WG, et al. Complex karyotype is a stronger predictor than del(17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens. *Cancer* 2015;121:3612–3621.
 52. Baliakas P, Iskas M, Gardiner A, et al. Chromosomal translocations and karyotype complexity in chronic lymphocytic leukemia: a systematic reappraisal of classic cytogenetic data. *Am J Hematol* 2014;89:249–255.
 53. Jaglowski SM, Ruppert AS, Heerema NA, et al. Complex karyotype predicts for inferior outcomes following reduced-intensity conditioning allogeneic transplant for chronic lymphocytic leukaemia. *Br J Haematol* 2012;159:82–87.
 54. Woyach JA, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. *Blood* 2014;123:1810–1817.
 55. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. *Blood* 2014;123:3390–3397.
 56. Coutre SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. *Leuk Lymphoma* 2015;56:2779–2786.
 57. Lampson BL, Kasar SN, Matos TR, et al. Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity. *Blood* 2016;128:195–203.

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Posttest Questions

1. Which of the following are appropriate for first-line therapy for patients aged ≥ 65 years with significant comorbidities?
 - a. Obinutuzumab + chlorambucil
 - b. Ibrutinib
 - c. Rituximab + chlorambucil
 - d. A and B
2. True or False: In patients aged < 65 years without significant comorbidities, FCR is the standard of care for first-line

therapy in patients without del(17p) or *TP53* mutations.

3. Which of the following are considered appropriate treatment options for relapsed/refractory CLL/SLL with del(17p) or *TP53* mutations?
 - a. Ibrutinib
 - b. Venetoclax
 - c. Idelalisib + rituximab
 - d. All of the above