Overview of the Recent Developments in Chronic Lymphocytic Leukemia, Part 1

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Background: The clinical development landscape for chronic lymphocytic leukemia (CLL) is evolving rapidly, and continuously challenges current therapeutic guidelines. Several new agents have recently gained approval from the US Food and Drug Administration and European Medicines Agency, including venetoclax, ibrutinib, idelalisib, and obinutuzumab. These new therapies, together with recent updates to the guidelines from the National Comprehensive Cancer Network and European Society for Medical Oncology, reflect findings of improved progression-free and overall survival rates, and represent a new age in the treatment of CLL.

Objective: The objective of this manuscript is to provide an overview of recent changes to the CLL landscape, as well as future directions to inform practitioners and clinical researchers.

Discussion: Because of these changes, it is likely that the future will bring further development of niche drugs that target cytogenetic abnormalities—specifically 11q and 17p—as well as more active and tolerable regimens for older patients. Tolerable regimens and convenient routes of administration are needed to enable outpatients to self-administer their treatment long-term, and improve their quality of life.

Conclusion: The increasing number of novel agents for CLL management present new challenges for appropriate sequencing of these agents, and comparator arm choices for future trials. Collaboration between developers can lead to more efficient and less costly clinical trials. Increased enrollment in clinical trials, especially among older patients, will be critical for the continued development of novel agents in the treatment of CLL.

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From 2005 to 2014, the number of ongoing trials of chronic lymphocytic leukemia (CLL) has increased at a compound annual growth rate of 18.4%.[1] This rapid growth in the CLL clinical trial landscape has led to multiple breakthroughs in the management of CLL, which have changed—and will continue to change—the treatment paradigm in the near future. One major breakthrough includes the discovery and development of agents targeting the B cell. CLL pathogenesis is a complex process that results in replication of malignant B lymphocytes. B-cell receptor signaling plays a role in B-cell survival and proliferation in CLL through the actions of protein kinases. The cells of CLL reportedly have high levels of B-cell receptor signaling activity.[2] Bruton tyrosine kinase (Btk) and phosphoinositide 3-kinase delta play important roles in this signaling process once the B-cell receptor is ligated. Once Btk is activated by the Src family kinases (Blk, Lyn, and Fyn), it activates phospholipase-Cγ through phosphorylation, which mobilizes internal calcium and activates the NF-κB and mitogen-activated protein kinase pathways. People with mutations in Btk have low levels of B cells and immunoglobulins. Inhibiting these kinases has demonstrated practice-changing efficacy in CLL.[3] With a better understanding of B-cell receptor signaling pathways, treatment and research focus has shifted from alkylating agents and purine analogs to alternate approaches, including targeting tyrosine kinase inhibitors and novel anti-CD20 monoclonal antibodies, which interfere with B-cell signaling. This transition has revolutionized CLL to a disease that is manageable, allowing some patients with the condition to live a normal lifespan. Ongoing trials are designed to demonstrate the optimal combinations and sequences of treatments, with the possibility of developing a curative regimen for select patients.

Several novel agents have recently received breakthrough therapy designation and subsequent approval from the US Food and Drug Administration (FDA). By the end of 2014, 17 medications designated as break-

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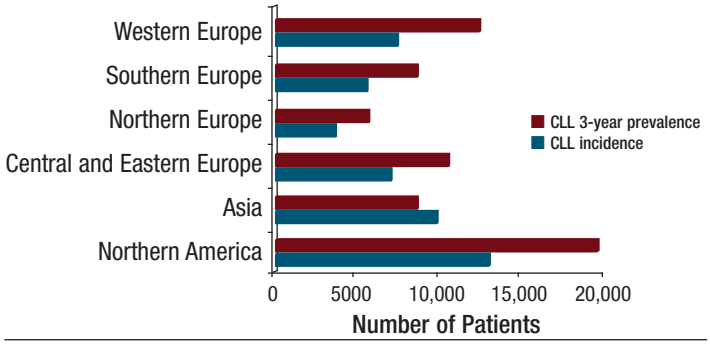
through therapies had gained FDA approval; 11 were approvals in hematology and oncology, with 4 indicated for patients with CLL. The latter include ibrutinib (Imbruvica; Pharmacyclics LLC, Sunnyvale, CA), idelalisib (Zydelig; Gilead Sciences, Inc, Foster City, CA), ofatumumab (Arzerra; Novartis Pharmaceuticals Corporation, East Hanover, NJ), and obinutuzumab (Gazyva; Genentech, Inc, South San Francisco, CA).[4] Ibrutinib received FDA approval in February 2014 for the treatment of patients with CLL who have received ≥1 previous therapies; in July 2014, accelerated approval was granted for a new indication: patients with CLL with 17p deletion/mutation (del17p). In March 2016, an additional expanded approval was granted to ibrutinib for the first-line treatment of CLL.[5] At the same time, idelalisib received FDA approval for the treatment of relapsed CLL in combination with rituximab. In April 2014, the anti-CD20 monoclonal antibody ofatumumab was granted FDA approval to expand its use to patients with untreated CLL for whom fludarabine-based therapy is inappropriate. The CD20-directed cytolytic antibody, obinutuzumab, gained approval in November 2013 for frontline treatment of patients with CLL in combination with chlorambucil. All 4 agents also received approval from the European Medicines Agency 2 to 3 months after the FDA approval. In addition, in April 2016, the FDA granted accelerated approval of venetoclax, a Bcl-2 inhibitor, for patients with CLL with del17p, and who have been treated with ≥1 prior therapies.[6]

Although these breakthrough therapies have dramatically improved outcomes, their cost to patients and society is not insignificant. Ibrutinib and idelalisib are oral medications that require continuous and indefinite daily use. The average wholesale price for a 12-month supply of these agents is approximately $118,000.[7] Because CLL is considered a disease of older adults, oral medications are covered by Medicare Part D in the United States. However, there are coverage gaps requiring significant out-of-pocket expenses, estimated to be $20,847 for a 30-month course of ibrutinib, and $14,449 for a 20-month course of idelalisib in the relapsed setting. The average wholesale price of obinutuzumab plus chlorambucil is $52,877 for 6 cycles of therapy; however, because obinutuzumab is an intravenous medication, it is covered by Medicare Part B in the United States, which does not have the same coverage gap as Part D. The estimated out-of-pocket expense for obinutuzumab and chlorambucil is $1179. Ofatumumab's average wholesale price is $124,332 for 6 cycles of therapy; however, because it is an intravenous medication, the out-of-pocket costs for patients with Medicare Part B are not significant. In the future, it is expected that idelalisib and ibrutinib will gain broad approval as first-line treatment of CLL, which will lead to an even greater cost burden for the patient. Out-of-pocket costs in Europe vary, with some medications undergoing pharmacoeconomic evaluation before becoming available (as is done by the National Institute for Health and Care Excellence in the United Kingdom).

Figure Chronic Lymphocytic Leukemia Incidence and 3-Year Prevalence Worldwide[a,b]



[a]CLL incidence comprises the absolute number of cases annually. Three-year prevalence represents the number of CLL patients diagnosed and alive after 3 years.

[b]To determine CLL epidemiology, this analysis includes WHO GLOBOCAN 2012 data. However, CLL epidemiology is not referenced in GLOBOCAN; therefore, the proportion of CLL case incidence and 3-year prevalence was calculated. CLL comprises approximately 30% of leukemia cases in Western countries and ~4%-10% of leukemia cases in Asia.

CLL indicates chronic lymphocytic leukemia.

Source: Reference 16.

This increase in approvals has created a dynamic clinical development landscape for CLL, including increasing competition of promising agents, a change in the standard of care, and more challenging regulatory hurdles. Sequencing, and the ideal combinations of novel-novel or novel-approved regimens, are considerations for future clinical trials. These new therapies have demonstrated better progression-free and overall survival rates than those of traditional chemotherapy regimens. Although these improvements bring hope to patients and practitioners, they also create challenges for future CLL drug development. The competition has increased the threshold for expected CLL efficacy and approval for future agents, because they will be compared with these newer agents. Thus, future studies are warranted to explore biomarkers or other surrogate end points, such as minimal residual disease status, which may further guide treatment and differentiate marketed products. Cytogenetics may also play an important role in future trials and their ability to identify the best drug for each patient. To address these challenges, collaborative efforts among pharmaceutical companies may be a novel and necessary direction of future CLL research.

Part 1 of this review was undertaken to provide better understanding of the future of CLL research. Our objective for the remainder of the series is to characterize CLL and its current treatments, compare newly approved drugs to traditional regimens, identify promising medications in development, and explore potential implications for CLL drug development.

Global Epidemiology of Chronic Lymphocytic Leukemia

CLL is the most common leukemia in Western countries, representing approximately 22% to 30% of all leukemias worldwide.[8,9] In certain Asian countries (eg, China, India, and Japan), the percentage of CLL cases is much lower (4%-10% of leukemias).[10-14] However, these countries have large populations, so the actual number of afflicted patients might be similar. The global annual incidence is between <1 and 5.5 per 100,000 people, and more men than women are affected.[10] The incidence of CLL is approximately 4.2 cases per 100,000 people in the Western world.[9,15] The global CLL incidence and 3-year prevalence are shown in the **Figure**.[16] This figure also shows that few countries have a large population with CLL, which brings to light potential challenges that arise when selecting countries and sites for studying CLL, especially in phase 3 trials. In addition to the low incidence/prevalence, there is intense competition for these patients. ■

Author Disclosure Statement

Dr Combest, Dr McAtee, and Dr Reitsma are employees of Pharmaceutical Product Development (PPD), Wilmington, NC. Dr Danford is a Research Fellow at PPD, and the University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC. Dr Andrews and Dr Simmons have no relevant disclosures to report.

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Overview of the Current Treatment Paradigm in Chronic Lymphocytic Leukemia, Part 2

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Background: The clinical development landscape for chronic lymphocytic leukemia (CLL) is evolving rapidly, and continuously challenges current therapeutic guidelines. Several new agents have recently gained approval from the US Food and Drug Administration and European Medicines Agency, including venetoclax, ibrutinib, idelalisib, and obinutuzumab. These new therapies, together with recent updates to the guidelines from the National Comprehensive Cancer Network and European Society for Medical Oncology, reflect findings of improved progression-free and overall survival rates, and represent a new age in the treatment of CLL. Part 1 of this series was published in this journal in June 2016.

Objective: The objective of this article is to provide an overview of recent changes to the CLL landscape, as well as future directions to inform practitioners and clinical researchers.

Discussion: Because of these changes, it is likely that the future will bring further development of niche drugs that target cytogenetic abnormalities—specifically 11q and 17p—as well as more active and tolerable regimens for older patients. Tolerable regimens and convenient routes of administration are needed to enable outpatients to self-administer their treatment long-term, and improve their quality of life.

Conclusion: The increasing number of novel agents for CLL management presents new challenges for appropriate sequencing of these agents, and comparator arm choices for future trials. Collaboration between developers can lead to more efficient and less costly clinical trials. Increased enrollment in clinical trials, especially among older patients, will be critical for the continued development of novel agents in the treatment of CLL.

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Chronic lymphocytic leukemia (CLL) is a disease that predominantly occurs in older adults; the median age at diagnosis is 71 years.[1] Therefore, the CLL population typically has age-related comorbidities. Although CLL may have a chronic natural history, the disease is incurable with currently available therapies, and disease course is variable, especially early in its evolution. Patients without an immediate requirement for treatment can defer treatment until disease progression occurs, or until justification for treatment arises, such as disease-related symptoms (eg, B-symptoms, which include fever, night sweats, and weight loss), threatened organ function, or symptoms specifically related to bulky disease.

A patient's age and comorbidities affect their ability to tolerate chemotherapy; therefore, age range (older or younger than age 70 years) and performance status are used in conjunction with prognostic factors to select initial treatment options for each patient. Prognostic factors for poor outcome include higher stage of disease at the time of diagnosis, shorter lymphocyte doubling time, diffuse bone marrow pattern, and certain cytogenetic abnormalities.

The most common cytogenetic abnormalities occur in chromosomes 12 or 14.[2] Worse outcomes are associated with deletion 17p (del17p), whereas patients with deletions of chromosome 11q (del11q) may have a favorable response to alkylator-based therapies (**Table**).[3] More favorable outcomes are associated with a sole deletion of 13q.[2] Furthermore, ZAP-70, an intracellular tyrosine kinase, and the degree of immunoglobulin heavy-chain variable gene mutation may help predict the aggressiveness of CLL.

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NOTE: This is part 2 of a 3-part series. Part 1 appeared in the June issue of the journal; part 3 will appear in the December issue.

Table Prognostic Factors for Chronic Lymphocytic Leukemia Relative to Time Until Progression

Prognostic factor	Interpretation
Flow cytometry	
CD38	Poor outcome (≥30%), favorable outcome (<30%)
ZAP-70	Poor outcome (≥20%), favorable outcome (<20%)
Cytogenetic abnormalities	
del17p	Poor outcome
del11q	Poor outcome, favorable response to alkylator-based therapies
Sole deletion of 13q	Favorable outcome
DNA sequencing	
IGHV	Poor outcome (≤2% mutation), favorable outcome (>2% mutation)

del11q indicates 11q deletion; del17p, 17p deletion; IGHV, immunoglobulin heavy-chain variable.
Source: Reference 3.

Current treatment guidelines initially recommend stratifying patients into 2 groups using fluorescence in situ hybridization cytogenetic testing: those with del17p/mutation, and those without del17p. Patients without del17p are further stratified based on age (ie, ≥70 or ≤69 years), comorbidities, and del11q status.[4] Historically, as first-line treatment, frail patients without del11q or del17p might have received chlorambucil (with or without rituximab), rituximab monotherapy, or pulse corticosteroids.

More recently, combination treatment with obinutuzumab and chlorambucil has become a preferred first-line regimen for frail patients with comorbidities, based on data from the CLL11 phase 3 trial, in which obinutuzumab and chlorambucil demonstrated significant and clinically relevant improvements in the rates of progression-free survival (PFS; 26.7 months vs 15.2 months); complete response (21% vs 7%); and minimal residual disease (MRD)-negative status (29.4% vs 2.5%) relative to rituximab and chlorambucil.[5] The median overall survival was not reached in the obinutuzumab and chlorambucil arm, versus 58.5 months in the chlorambucil arm (hazard ratio, 0.62; 95% confidence interval, 0.42-0.92), based on updated survival results presented at the 57th American Society of Hematology Annual Meeting and Exposition in 2015.[6]

Another preferred regimen in this population is ibrutinib as a single agent. In general, older patients—and patients who are younger but have comorbidities—may be treated with a variety of single- or multiple-agent chemotherapies, immunotherapies, or chemoimmunotherapy. The combination of obinutuzumab and chlorambucil, and ibrutinib as a single agent recently emerged as the preferred regimens, according to the 2016 update to the treatment guidelines of the National Comprehensive Cancer Network (NCCN).[3] However, in the clinical setting, initial use of obinutuzumab and chlorambucil in older patients has not been common practice.[7] The ibrutinib category 1 recommendation was added in version 2 of the 2016 NCCN guidelines, so prescribing uptake is yet to be determined.[3]

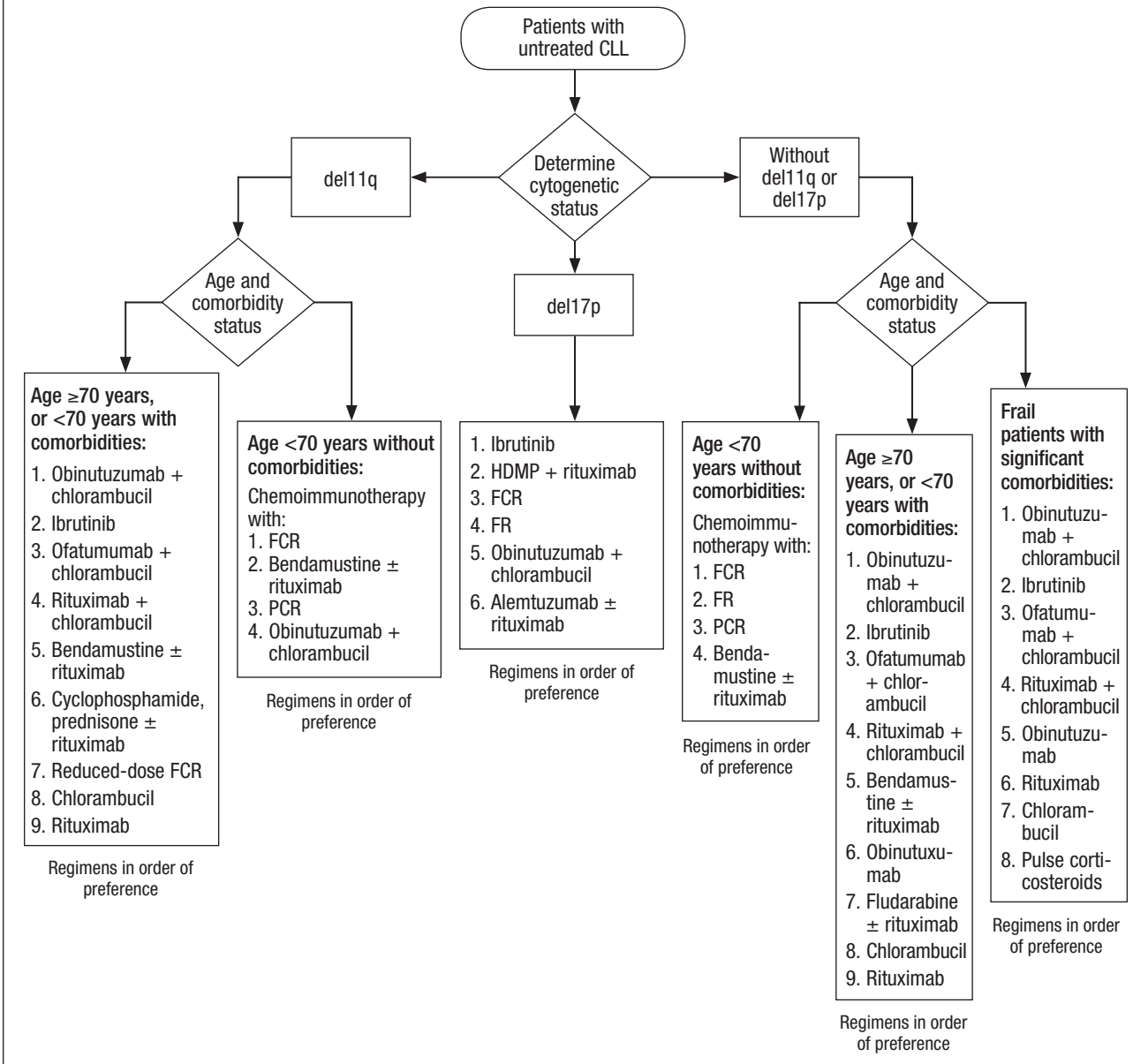
Another potential option for first-line treatment in older patients or younger patients with significant comorbidities is ofatumumab combined with chlorambucil. Although ofatumumab's current role is limited in CLL, it has been an option in this setting since improvement versus chlorambucil alone in median PFS was demonstrated in the COMPLEMENT1 trial (22.4 months vs 13.1 months for chlorambucil alone).[8] Comparing results for the CLL11 and COMPLEMENT1 trials, it appears that obinutuzumab may be slightly more active than ofatumumab (PFS, 26.7 months vs 22.4 months, respectively); however, serious infusion reactions during the first cycle are more common with obinutuzumab.

Younger patients without comorbidities (or del17p) should receive chemoimmunotherapy, usually including a purine-antimetabolite and rituximab, as shown in **Figure 1**.[3] Regimens can include fludarabine, cyclophosphamide, and rituximab (FCR); fludarabine and rituximab (FR); pentostatin, cyclophosphamide, and rituximab (PCR); bendamustine alone or in combination with rituximab (BR); or obinutuzumab plus chlorambucil.

The CLL8 trial demonstrated that adding rituximab to fludarabine and chlorambucil (FC) improved the median PFS period (51.8 months vs 32.8 months) and the overall survival rate (69.4% vs 62.3% at 5.9 years' follow-up).[7,9]

In another study, the median overall survival in the FC arm was 86 months, and was not reached in the FCR arm.[8] In the frontline setting, the CLL10 trial demonstrated that FCR was superior to BR in young, previously untreated, fit patients with advanced CLL.[10] The CR and MRD-negative rates were 40.7% versus 31.5%, and 74.1% and 62.9% in the FCR and BR arms, respectively. The median PFS period was significantly longer in the FCR arm than in the BR arm (53.7 months vs 43.2 months). The 36-month overall survival rate differed only minimally between the arms (90.6% in the FCR arm and 92.2% in the BR arm). Severe neutropenia and infections were more common in the FCR arm, especially in older patients. Because toxicity was higher in older patients, dose reductions

Figure 1 Clinical Treatment Pathway for Patients with Untreated CLL

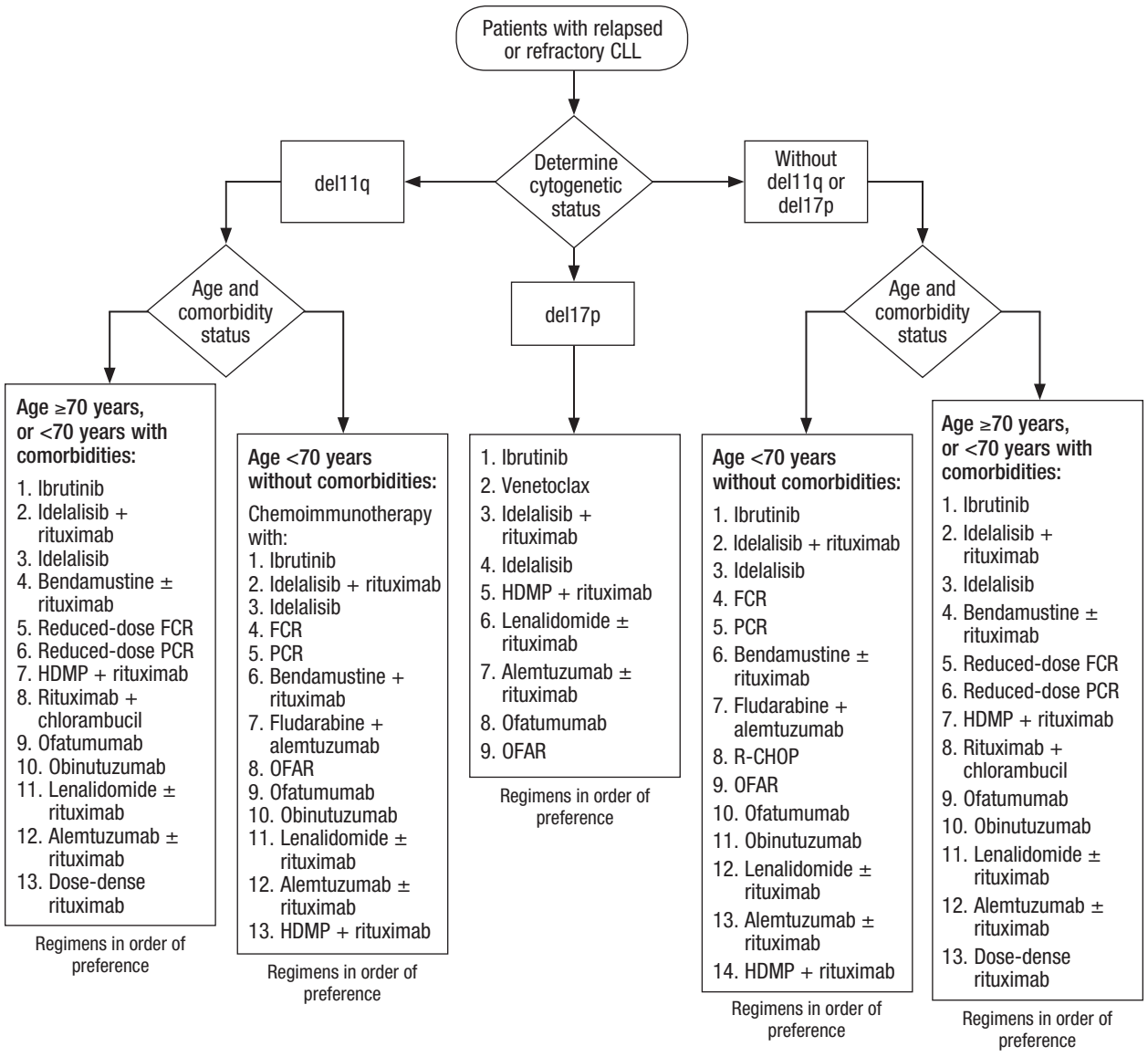


CLL indicates chronic lymphocytic leukemia; del11, 11q deletion; del17p, 17p deletion; FCR, fludarabine, cyclophosphamide, rituximab; FR, fludarabine, rituximab; HDMP, high-dose methylprednisolone; PCR, pentostatin, cyclophosphamide, rituximab.
Source: Reference 3.

led to similar efficacy between both regimens. Although FCR is the current standard therapy for very fit, younger patients, obinutuzumab and chlorambucil, ibrutinib, or BR are more appropriate regimens for older patients with CLL, or patients with significant comorbidities and CLL.[3]

Patients with del17p respond poorly to current treatment; therefore, ibrutinib in the first-line setting, and the recently approved BCL-2–selective inhibitor venetoclax (ABT-199) in the relapsed and refractory setting, may be warranted. In patients with complex karyotype (≥3 abnormalities), following a response to ibrutinib, allogeneic stem-cell transplantation, or enrollment into a clinical trial should be considered before progression.

Figure 2 Clinical Treatment Pathway for Patients with Relapsed or Refractory CLL



CLL indicates chronic lymphocytic leukemia; del11, 11q deletion; del17p, 17p deletion; FCR, fludarabine, cyclophosphamide, rituximab; HDMP, high-dose methylprednisolone; OFAR, oxaliplatin, fludarabine, cytarabine, and rituximab; PCR, pentostatin, cyclophosphamide, rituximab; R-CHOP, rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone.
Source: Reference 3.

Patients with del11q respond better to alkylating treatment, and may preferentially receive such therapy. Some of these patients may become eligible for allogeneic stem-cell transplantation (Figure 1).[3]

In the relapsed or refractory setting, ibrutinib monotherapy or idelalisib plus rituximab are recommended irrespective of age, comorbidities, or cytogenetics; venetoclax is also being recommended (category 2A per version 3.2016 NCCN guidelines) as an option for patients with del17p (**Figure 2**).[3] A cross-trial comparison of these 2 regimens (ie, ibrutinib alone and idelalisib plus rituximab) shows that the PFS and overall survival rates are essentially the same. Both options are acceptable, and recommended treatment will depend on mul-

tiple patient parameters, including previous therapy. One major consideration is the recent safety alert regarding idelalisib, as well as the tolerability profile of idelalisib in general.[3]

All 6 ongoing idelalisib trials were stopped amid an increased rate of adverse events, specifically deaths related to *Pneumocystis jiroveci* pneumonia and cytomegalovirus infection. The current US Food and Drug Administration and European Medicines Agency recommendation is to continue to use idelalisib in patients who are benefiting, but closely monitor them for signs of infection. In addition, all patients should receive prophylaxis for *P jiroveci* pneumonia during idelalisib treatment.

As a precaution while the data are being reviewed, idelalisib should not be started as first-line treatment in patients with CLL who have del17p. However, use of idelalisib can be continued in combination with rituximab in patients with relapsed or refractory CLL. The regimen with the best historical PFS period and overall survival rate in previously treated patients with CLL is ibrutinib in combination with BR from the HELIOS phase 3 trial; however, this is not an NCCN-recommended regimen as of the last guideline update (version 2.2016).[4,11]

In fludarabine-refractory CLL—defined by a relapse within 6 months of the last treatment—single-agent options include ibrutinib or rituximab. Combination options for fludarabine-refractory CLL include ibrutinib and bendamustine, or idelalisib and rituximab. Enrolling in a clinical trial is another good option in this setting. Venetoclax alone or in combination with other therapies should be considered.

In a phase 1/2 venetoclax dose-escalation trial, 57% of patients had fludarabine-refractory CLL.[12] The overall response rate in fludarabine-refractory CLL was 79%, which included several patients with MRD-negative status. In the overall population and fludarabine-refractory subgroup, venetoclax induced a high rate of durable remissions.[12]

Allogeneic hematopoietic stem-cell transplantation (HSCT) for curative intent is another option for eligible patients with fludarabine-refractory CLL. Although controversial in CLL treatment, HSCT following maximum response to a novel targeted therapy—ibrutinib with or without rituximab, and bendamustine, idelalisib, and rituximab, or venetoclax—is an option that should be considered over continuation of targeted therapy. Although complete responses are not particularly common (up to 21.4% with ibrutinib, bendamustine, and rituximab, and 22% with venetoclax), deep remission (ie, significant reduction in disease burden) and MRD-negative disease are possible with these regimens.[11,12] Some considerations before choosing HSCT include access to novel therapies (and their cost), previous treatments, cytogenetics and disease risk, donor match, physiologic age and comorbidities, and patient goals.[13]

These promising new therapies are not without toxicity, and the decision to select a particular regimen should also take into account the adverse event profile of each agent. Because CLL is a disease predominantly of older adults, treatment can be complicated by comorbidities and performance status. Although ibrutinib is generally well-tolerated (common adverse events include fatigue, diarrhea, infection, cytopenia, cough, rash, and arthralgia), the slightly greater risk of atrial fibrillation is a relevant concern for older patients. The bleeding risk associated with ibrutinib is rare, but there is a potential concern in patients on anticoagulation therapy for comorbid conditions such as atrial fibrillation, venous thromboembolism, and valvular heart disease.[14]

Common adverse events in response to idelalisib include fatigue, diarrhea, colitis, nausea, hypertension, pneumonitis, edema, and elevated liver transaminase values, so close monitoring of hepatic function at baseline and during therapy is required. Close monitoring for pulmonary symptoms such as cough, dyspnea, and bilateral infiltrates is also required. Currently, all patients receiving idelalisib must receive prophylaxis for *P jiroveci* pneumonia and cytomegalovirus, and be closely monitored for signs of infection.[15]

The most common adverse events related to obinutuzumab treatment include serious infusion reactions (especially during the first cycle), neutropenia, and thrombocytopenia. Infusion reactions are anticipated during the first cycle and can be managed; however, the severity of such reactions can be a concern for older patients, particularly because obinutuzumab plus chlorambucil is considered the standard of care for untreated older patients or patients with comorbidities. With venetoclax, specific tumor lysis syndrome prophylaxis and monitoring are recommended, based on tumor burden.[3]

Prophylaxis includes 1.5 to 2 L of oral hydration—with intravenous hydration in patients with medium and high tumor burden—with allopurinol. Rasburicase is reserved as an option if baseline uric acid levels are elevated in patients with high tumor burden. Frequent blood chemistry monitoring following venetoclax administration is also warranted, with inpatient monitoring during the first dose for patients with high tumor burden or poor renal function.

The most frequently prescribed first-line regimens for untreated patients include FCR, BR, chlorambucil (with or without rituximab or obinutuzumab), or rituximab monotherapy (common in the United States). The popularity of prescribing obinutuzumab has been slower than expected since it was demonstrated in 2013

that the combination of obinutuzumab and chlorambucil achieved superior PFS rates and other outcome measures compared with chlorambucil alone, and versus the combination of rituximab and chlorambucil.[16]

Chlorambucil is an established and frequently used therapy (as monotherapy or in combination with rituximab or obinutuzumab), and is generally used for patients with comorbidities who are not fit to receive fludarabine-based regimens—including FCR—or if aggressive treatment is not indicated. However, use of chlorambucil as monotherapy in the frontline setting is no longer considered standard of care based on results of the CLL11 trial, and should no longer be used as a control regimen in clinical trials.

In the past, prescribing patterns have closely aligned with evidence-based first-line treatment algorithms. However, a recent survey of hematology-oncology physicians showed that prescribers have been slow to adopt newer treatment modalities despite their inclusion as first-line options in treatment guidelines, opting instead for BR as first-line therapy in 43% to 67% of cases.[7]

Moreover, most new targeted therapies for relapsed or refractory populations were approved in a short time span, between the end of 2013 and July 2014, and were only recently approved and recommended for first-line use. Therefore, these agents are generally not yet widely available and approved as first-line agents.

As the use of ibrutinib, idelalisib, venetoclax, and other targeted therapies is transitioned from patients with relapsed or refractory CLL to those with untreated CLL, and these drugs become approved for first-line treatment in all patients—not only those with del17p or those who are older or frail—it is likely that prescribing practices will change substantially.

In Europe, use of newer agents has been slow because reimbursement decisions by national health authorities are often delayed long after approval. Furthermore, in the South American countries surveyed, access to the new agents beyond compassionate use or expanded-access programs was limited because reimbursement was not provided as of early 2015. ■

Author Disclosure Statement

Dr Combest, Dr McAtee, and Dr Reitsma are employees of Pharmaceutical Product Development (PPD), Wilmington, NC. Dr Danford is a Research Fellow at PPD, and the University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC. Dr Andrews and Dr Simmons have no relevant disclosures to report.

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Overview of the Current Development Landscape in Chronic Lymphocytic Leukemia, Part 3

Austin J. Combest, PharmD, BCOP, MBA; Ryan C. Danford, PharmD; Elizabeth R. Andrews, PharmD; Ashley Simmons, PharmD; Paulina McAtee, PharmD; Dirk J. Reitsma, MD

Background: The clinical development landscape for chronic lymphocytic leukemia (CLL) is evolving rapidly, and continuously challenges current therapeutic guidelines. Several new agents have recently gained approval from the US Food and Drug Administration and European Medicines Agency, including venetoclax, ibrutinib, idelalisib, and obinutuzumab. These new therapies, together with recent updates to the guidelines from the National Comprehensive Cancer Network and European Society for Medical Oncology, reflect findings of improved progression-free and overall survival rates, and represent a new age in the treatment of CLL. This is the last part of a 3-part series.

Objective: The objective of this 3-part article is to provide an overview of recent changes to the CLL landscape, as well as future directions to inform providers and clinical researchers.

Discussion: Because of these changes, it is likely that the future will bring further development of niche drugs that target cytogenetic abnormalities, specifically 11q and 17p deletion, as well as more active and tolerable regimens for older patients. Tolerable regimens and convenient routes of administration are needed to enable outpatients to self-administer their treatment long-term, and improve their quality of life.

Conclusion: The increasing number of novel agents for CLL management presents new challenges for appropriate sequencing of these medications, and comparator arm choices for future clinical trials. Collaboration between drug developers can lead to more efficient and less costly clinical trials. Increased enrollment in clinical trials, especially among older patients, will be critical for the continued development of novel agents for the treatment of CLL.

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Part 3 of a 3-part series

Disclosures are at end of text

The chronic lymphocytic leukemia (CLL) development landscape is one of the most dynamic areas in oncology clinical research. During the writing of this manuscript, there were new approvals made, and guidelines were updated. Ibrutinib received an expanded approval for the first-line treatment of CLL in March 2016, and venetoclax received accelerated approval for patients with CLL with 17p deletion (del17p) and who have been treated with ≥1 previous therapies.[1,2]

In February 2014, ibrutinib was approved by the US Food and Drug Administration (FDA) for patients with CLL who had received ≥1 previous treatments, as a result of its superiority over ofatumumab with respect to the progression-free survival (PFS) period (median not reached vs 8.1 months; hazard ratio [HR], 0.22), and the overall survival (OS) rate (84% vs 67%; HR, 0.43).[3] In July 2014, the FDA granted accelerated approval of ibrutinib for use in patients with del17p.

Also in July 2014, idelalisib received FDA approval for the treatment of patients with relapsed CLL in combination with rituximab. This approval was based on a 220-patient phase 3 clinical trial that was terminated early because of a significant difference in the PFS rate at 24 weeks (93% vs 46%; P <.001). The accelerated approval allowed the use of the drug in patients with relapsed CLL or with small lymphocytic lymphoma who had received ≥2 previous therapies, based on an overall response rate of 57% and a median time to response of 1.9 months for a variety of indolent non-Hodgkin lymphomas.

The initial PFS and OS curves (**Figures 1-4**) show the very promising results of ibrutinib and idelalisib in the untreated and relapsed or refractory patient populations.[3-18] Longer follow-up is needed to confirm the durability of these promising results and to determine whether resistance to these agents develops over time.

Ongoing or planned phase 3 clinical trials will expand the role of targeted therapy with ibrutinib and idelalisib in CLL treatment by testing it in combination regimens containing bendamustine, rituximab, cyclophosphamide, obinutuzumab, or ofatumumab in patients with untreated and relapsed or refractory CLL. In addition,

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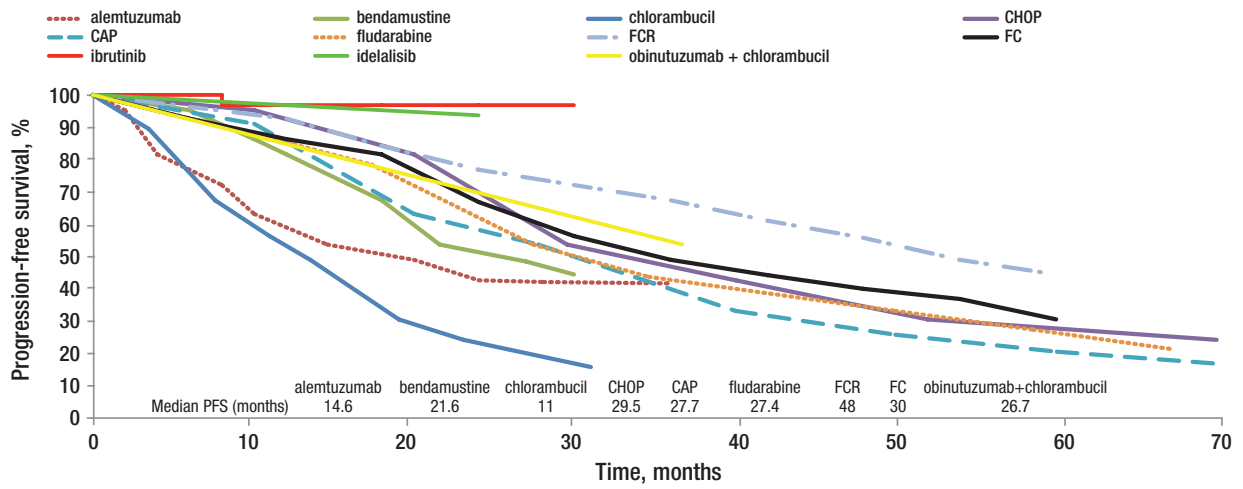
Figure 1 Progression-Free Survival: Treatment-Naïve Patients[a]

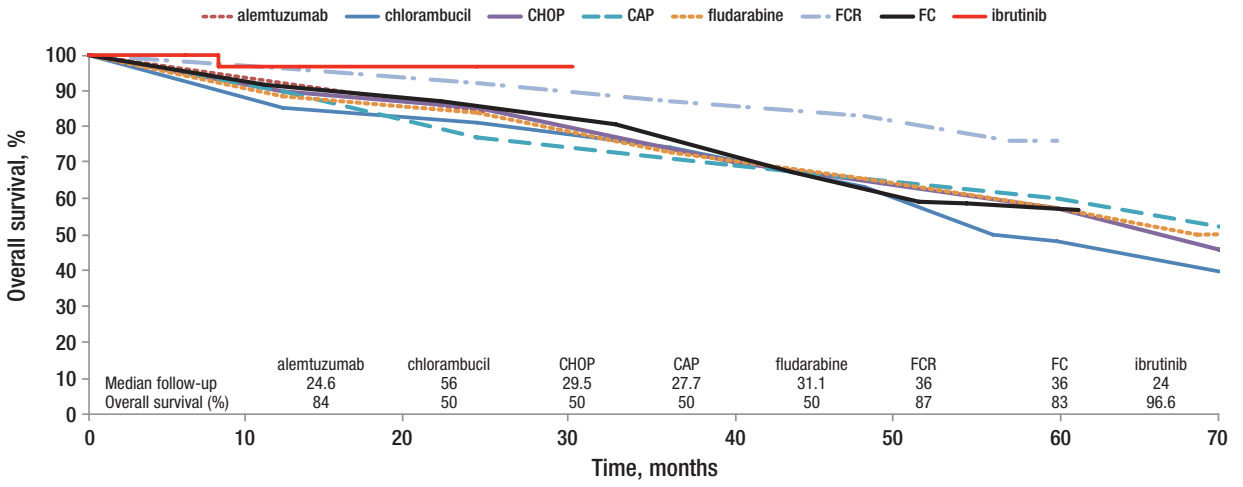


[a]PFS for each regimen is displayed at the bottom of the survival curve. Median PFS time is not listed for ibrutinib and idelalisib because reported phase 1/2 results have not yet reached PFS. Ofatumumab PFS data currently are not published or reported. PFS curves were recreated from published literature using median PFS and point estimates from Kaplan-Meier curves. For regimens evaluated in multiple trials, PFS data were calculated using a weighted average based on the number of patients in each trial.

CAP indicates cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), prednisone; FC, fludarabine, cyclophosphamide; FCR, fludarabine, cyclophosphamide, rituximab; PFS, progression-free survival.

Sources: References 4-11.

Figure 2 Overall Survival: Treatment-Naïve Patients[a]

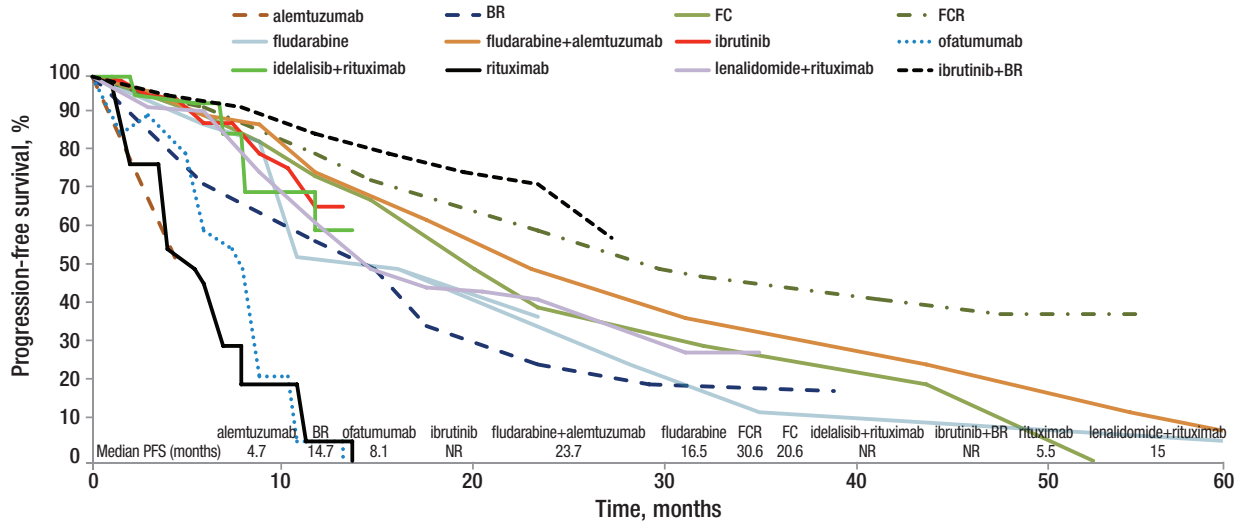


[a]OS (percentage) at median follow-up duration (months) is displayed below the OS curves. Preliminary OS data for untreated patients is not yet available for idelalisib, obinutuzumab, or ofatumumab. OS curves were recreated from published literature using median OS and point estimates from Kaplan-Meier curves. For regimens evaluated in multiple trials, OS data were calculated using a weighted average based on the number of patients in each trial.

CAP indicates cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), prednisone; FC, fludarabine, cyclophosphamide; FCR, fludarabine, cyclophosphamide, rituximab; OS, overall survival.

Sources: References 5-10.

Figure 3 Progression-Free Survival: Patients with Relapsed and/or Refractory Chronic Lymphocytic Leukemia[a]



[a]The PFS data presented are from phase 3 trials, other than for alemtuzumab, BR, and lenalidomide-rituximab (for which phase 2 data are presented). Data depict PFS specifically, except for BR and lenalidomide-rituximab (for which EFS and TTF are depicted). PFS curves were recreated from published literature using median PFS and point estimates from Kaplan-Meier curves.
BR indicates bendamustine and rituximab; CLL, chronic lymphocytic leukemia; EFS, event-free survival; FC, fludarabine, cyclophosphamide; FCR, fludarabine, cyclophosphamide, rituximab; NR, not reached; PFS, progression-free survival; TTF, time-to-treatment failure.
Sources: References 3, 12-18.

entospletinib (GS-9973), a spleen tyrosine kinase inhibitor, is currently being studied in 2 phase 2 clinical trials for relapsed or refractory CLL; one of the trials entails testing it in combination with idelalisib.

There is much excitement surrounding inhibitors of B-cell receptor signaling, including Bruton's tyrosine kinase (BTK) inhibitors (CC-292, ONO-4059, and ACP-196), phosphoinositide 3-kinase (PI3K)-delta inhibitors (idelalisib, IPI-145, and duvelisib), and spleen tyrosine kinase inhibitors. These molecules stop migration and adherence to the CLL microenvironment and promote cellular apoptosis. Two of the most promising agents are venetoclax, which was recently approved for CLL, and IPI-145, an investigational PI3K inhibitor.

Venetoclax was developed through reengineering another BCL-2 inhibitor, navitoclax. Like venetoclax, navitoclax showed therapeutic potential but was hampered by dose-limiting thrombocytopenia caused by BCL-X_L inhibition. By improving the selectivity of venetoclax for BCL-2 and decreasing off-target binding at BCL-X_L, thrombocytopenia is avoided.[14] Both CC-292 and ACP-196 are more potent than ibrutinib and may have a better tolerability profile.

Similar to chronic myelogenous leukemia (CML)—for which second-generation BCR-ABL inhibitors became available after the approval of imatinib and are now part of the CML armamentarium—there is room in the CLL landscape for next-generation BTK inhibitors.

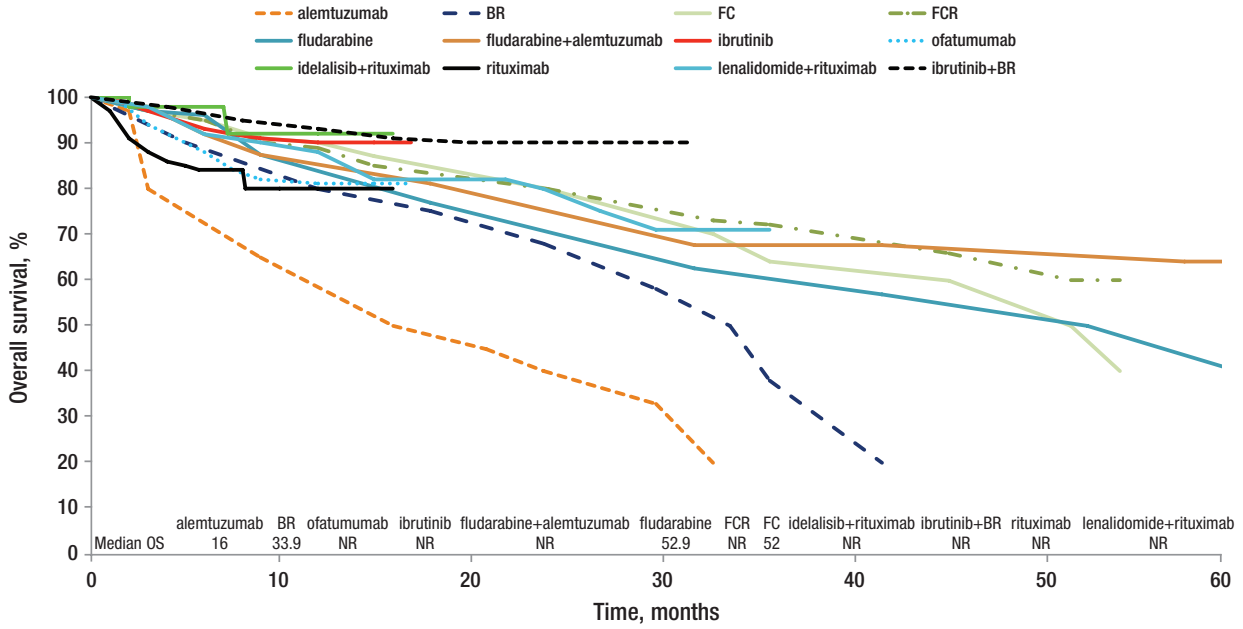
Although the hurdle for activity is now much higher, novel agents that are as or more effective than ibrutinib, idelalisib, and obinutuzumab, with superior safety and tolerability profiles, are needed. Also important is the need for active agents in patients with poor-risk cytogenetics (del17p or *TP53* mutation). New drugs in development may have a major impact on the therapeutic landscape of CLL, by increasing the available therapeutic options and by expanding therapeutic combinations and sequencing options (**Table**).[3,16-23]

In addition to the targeted agents, checkpoint inhibitors have become breakthrough therapies in solid tumors (eg, lung cancer) and are now being investigated in CLL. A planned phase 1/2 trial of durvalumab is currently in progress. Chimeric antigen receptor T-cells targeting CD19 (CTL019) have induced deep, long-term remissions in patients with relapsed or refractory CLL.[10] These promising immunotherapies may be the next treatment strategy for CLL. More research will be needed to identify the best combinations and the patients who are most likely to have deep molecular remissions and responses.

Clinical Trials Landscape

To better evaluate the importance of present evolu-

Figure 4 Overall Survival: Patients with Relapsed and/or Refractory Chronic Lymphocytic Leukemia[a]



[a]The OS data presented are from phase 3 trials, except for alemtuzumab, BR, and lenalidomide-rituximab (for which phase 2 data are presented). OS curves were recreated from published literature using median OS and point estimates from Kaplan-Meier curves.

BR indicates bendamustine and rituximab; FC, fludarabine, cyclophosphamide; FCR, fludarabine, cyclophosphamide, rituximab; NR, not reached; OS, overall survival.

Sources: References 3, 12-18.

tion in the therapeutic CLL landscape, we examined the number of ongoing, global phase 1 to phase 4 CLL trials, and the cumulative number of completed phase 1 to phase 4 trials. The compound annual growth rates of phase 1, 2, 3, and 4 clinical trials from 2005 to 2014 were 47.42%, 6.98%, 13.69%, and 83.33%, respectively.[24] At the time this article was written, there were 116 phase 1, 2, and 3 clinical trials planned or ongoing worldwide in the treatment setting for CLL. This number includes 14 phase 1, 83 phase 1/2 or phase 2, and 19 phase 2/3 or 3 studies. More than half (79) of these trials are in the United States; however, Canada, Europe (France, United Kingdom, Germany), and Asia Pacific (Australia, New Zealand) are also heavily involved.

The United States has the highest number (8) of phase 3 trials, and is also participating in 46 phase 2 trials, and 12 phase 1 trials. Fewer phase 1 trials are ongoing than phase 2 and phase 3 trials, which could indicate that fewer new agents are being investigated, or that many trials may involve testing multiple combinations of novel and established drugs (**Figures 5, 6**).[24]

For relapsed or refractory CLL, 100 phase 1 studies, 189 phase 1/2 or phase 2 studies, and 22 phase 2/3 or phase 3 studies are planned or ongoing. Similar to studies of CLL, most of the studies for relapsed or refractory CLL are conducted in the United States and Europe, with the majority being done in the United States (86 phase 1, 87 phase 2, and 13 phase 3). Australia is the most involved country in the Asia Pacific region, conducting 7 phase 3 and 2 phase 2 studies. Each year, the number of ongoing and completed CLL trials continues to increase.

Based on this development landscape and the global epidemiology of untreated and relapsed or refractory CLL, it is likely that CLL research will undergo a drastic change in coming years. Countries such as Ireland and some in the Asia Pacific region (eg, India, Russia, and China) may be of particular interest for new studies, because intense competition for sites and a changing standard of care necessitate relocation to countries where there are few directly competing trials. Opening up sites in smaller, less traditional countries may be beneficial for obtaining more treatment-naïve patient populations and minimizing competition; however, this must be weighed against the added startup costs of using an additional country.

Although CLL incidence is low in Asian countries, large population centers in these regions may provide

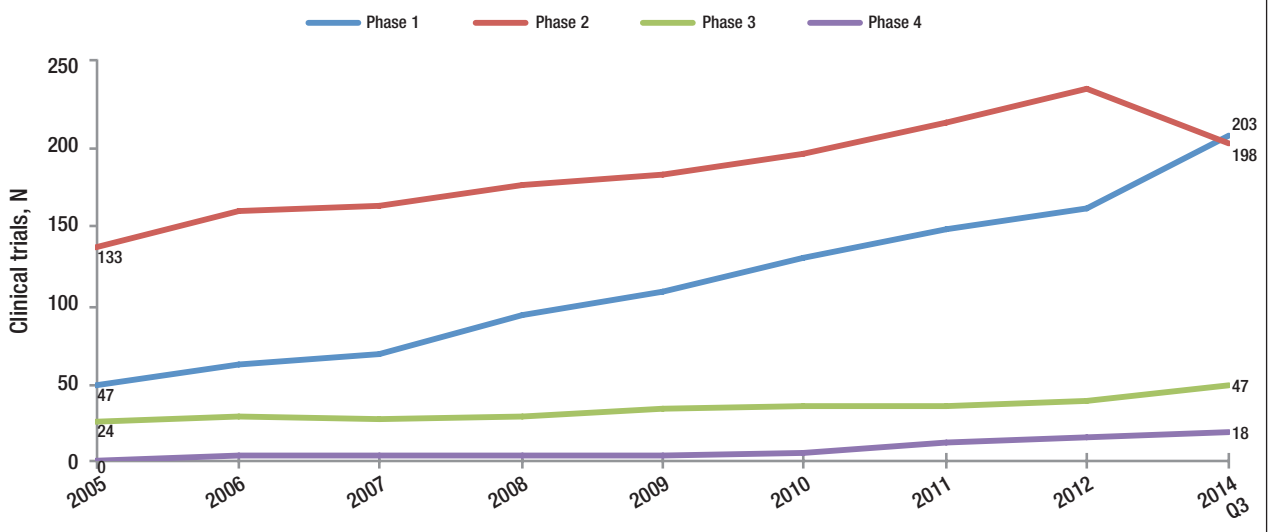
Table Summary of Pivotal CLL Clinical Trials[a]

Study regimen	Comparator(s)	Study design	Primary outcome	Progression-free survival	Overall survival
Pivotal CLL clinical trial summary: untreated patients					
Alemtuzumab[16]	Chlorambucil	Phase 3 Randomized International Open-label 297 patients	PFS	Alemtuzumab, 14.6 mo Chlorambucil, 11.7 mo HR: 0.58	84% at 24.6 mo
Bendamustine[17]	Chlorambucil	Phase 3 Randomized 319 patients	PFS ORR	Median PFS (P <.0001): Bendamustine, 21.6 mo Chlorambucil, 8.3 mo	Further follow-up required; currently no significant differences
Chlorambucil[18]	Fludarabine	Phase not specified Randomized Crossover 509 patients	PFS OS	Median PFS (P <.001): Chlorambucil, 14 mo Fludarabine, 20 mo	Median OS (not significantly different): Chlorambucil, 56 mo Fludarabine, 66 mo
CHOP[19]	CAP Fludarabine	Phase not specified Randomized 938 patients Median follow-up: 70 mo	OS	Median PFS (not significantly different): CHOP, 29.5 mo CAP, 27.7 mo Fludarabine, 31.7 mo	5-year OS (not significantly different): CHOP, 57.3% CAP, 59.8% Fludarabine, 58.4%
FCR[20]	FC	Phase 3 Randomized Open-label	PFS	3-year PFS (P <.0001): FCR, 65% FC, 45%	3 year OS (P = .01): FCR, 87% FC, 83%
Results for newly approved targeted therapies: patients with relapsed or refractory CLL					
Ibrutinib[3]	Ofatumumab	Phase 3 Randomized Open-label 391 patients	PFS	6-mo PFS: Ibrutinib, 88% Median PFS: Ofatumumab, 8.1 mo Ibrutinib, not reached HR, 0.22	12-mo OS (HR, 0.43): Ibrutinib, 90% Ofatumumab, 81%
Idelalisib-rituximab[21]	Rituximab	Phase 3 Randomized Double-blind 220 patients	PFS	Median PFS (HR, 0.15): Idelalisib-rituximab, not reached Rituximab, 5.5 mo	12-mo OS (HR, 0.28): Idelalisib-rituximab, 92% Rituximab, 80%
Preliminary results for new targeted therapies: untreated patients					
Ibrutinib[22]	—	Phase 1b/2 Open-label 31 patients	Safety	24-mo PFS estimate: Ibrutinib, 96.3%	24-mo OS estimate: Ibrutinib, 96.6%
Idelalisib-rituximab[23]	—	Phase 2 50 patients	ORR	24-mo PFS estimate: Idelalisib-rituximab, 91%	—

[a]A phase 2 study of the selective phosphatidylinositol 3-kinase delta inhibitor (PI3Kδ) idelalisib (GS-1101) in combination with rituximab in treatment-naïve patients aged >65 years with CLL or with small lymphocytic lymphoma.

CAP indicates cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine), prednisone; CLL, chronic lymphocytic leukemia; FC, fludarabine, cyclophosphamide; FCR, fludarabine, cyclophosphamide, rituximab; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Figure 5 Number of Ongoing Global Phase 1-4 Clinical Trials of CLL, 2005-2014[a]



[a]The increased number of phase 1 and phase 2 trials, coupled with recent positive results and approvals, may translate into a relative increase in phase 3 and 4 trials in 2015. Although the number of phase 2 trials appears to have trended downward since 2012, data for 2014 do not include Q4 statistics. Phase 3 trials have remained relatively constant since 2005.
CLL indicates chronic lymphocytic leukemia.
Source: Reference 24.

access to a large number of patients, including those who have not previously participated in clinical trials. Sites in metropolitan areas may be good targets that have low competition. In addition, a movement toward precompetitive collaborations among multiple pharmaceutical companies and academic centers is already in progress, and the scope of these collaborations is likely to increase in the future.

Feasibility of Clinical Trials in a Shifting Therapeutic Landscape

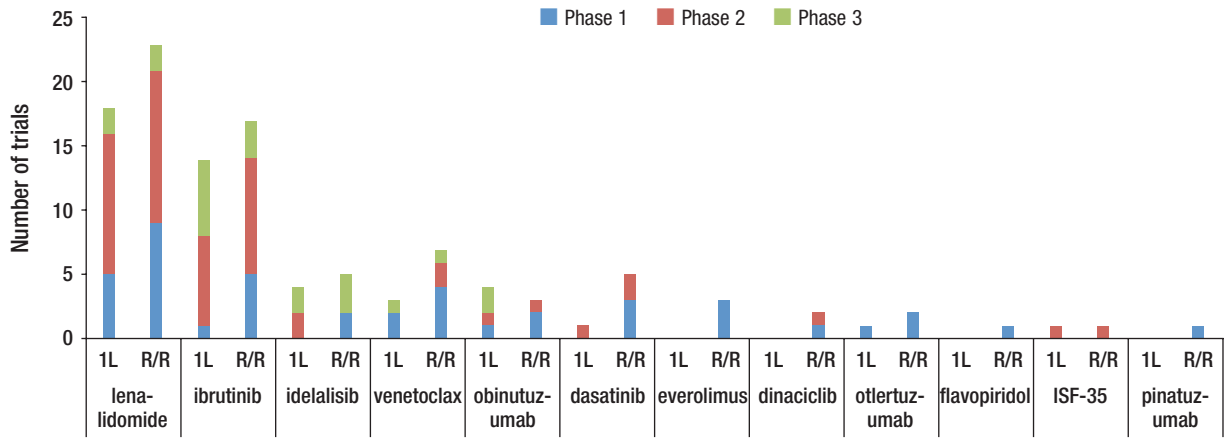
Based on experience and shared intelligence from previous phase 3 trials in CLL, the largest barrier to patient enrollment is the ability and willingness of participating sites and/or countries to use the required concomitant chemotherapy or immunotherapy. With a shifting standard of care in the untreated (bendamustine in combination with rituximab vs fludarabine, cyclophosphamide, and rituximab, ibrutinib, obinutuzumab, and chlorambucil) and the relapsed or refractory settings (venetoclax, ibrutinib, and idelalisib), a careful regional analysis is required before initiating a CLL trial.

Preliminary feasibility analysis is also required. Some countries do not have access, or have only limited access (ie, compassionate use), to the chemotherapeutic agents designated by the study protocol. In recent CLL trials, this difficulty was seen as a result of either eligibility requirements for the previous use of rituximab or bendamustine, or of protocols requiring the inclusion of certain medications in the treatment regimen that might not have been available in a specific region.

These issues may be compounded by different standards of care in certain regions, reimbursement issues, or the regulatory approval status of specific products. Moreover, some investigators may prefer to use standard-of-care regimens or a competing research protocol that they believe will show the same benefit, with reduced toxicity than what is currently being offered. A final barrier to enrollment may be the investigator's perceived ability to enroll the required number of patients. Except for the 10 to 15 countries with the highest prevalence of CLL, the population of patients declines significantly, and, thus, committing to enroll patients at a set rate may not be realistic.[12]

Although the focus of CLL research has become more personalized with respect to the patient's age, performance status, and cytogenetics, recruitment and early clinical trial matching programs may help determine patient eligibility. Overall, when planning a global CLL trial, strong consideration should be given to the availability of required concomitant medications or previous therapies, and the willingness or ability of the investigator to use those medications. Sites should be supported in their enrollment efforts, and be educated on protocols that may be more CLL subtype-specific.

Figure 6 Select Drugs in Development (Planned or Ongoing Clinical Trials) for Untreated or for Relapsed and/or Refractory CLL, as of October 2014[a]



[a]Lenalidomide, which is not a new agent, is currently being used the most in phase 1 and 2 clinical trials for CLL. Ibrutinib and idelalisib currently dominate the competitive phase 3 clinical trials landscape. Their promising results in patients with R/R CLL are leading to studies in untreated patients, alone and in combination with other agents. Listed compounds include novel agents as well as agents approved for other indications but for which expanded labeling for CLL is sought.

CLL indicates chronic lymphocytic leukemia; R/R, relapsed and/or refractory; 1L, untreated.

Source: Reference 24.

Conclusion: Clinical Implications of the Evolving Treatment Landscape of CLL

Different clinical development strategies, such as the parallel development of companion diagnostics or the use of precompetitive (or collaborative) clinical trials, should be given consideration for future efforts aimed at managing CLL. Such trials may use adaptive trial designs and Bayesian methods in phase 1/2 settings to assign patients to one of several treatment arms. Each arm could consist of a different agent, combination of agents, or sequence of agents, and comparisons could be made with shared control arms, because patients with different prognostic features may enroll.

This approach could shed light on ways to optimize treatment, conserve resources, and advance our knowledge of CLL treatment faster than the disparate approaches currently being used. With the increased pressure on pharmaceutical companies and contract research organizations to meet enrollment goals in clinical trials, and the increased pressure on investigators and site resources, this strategy may be more efficient for identifying which drugs work best for which patients. With such a dramatic shift in treatment patterns, novel–novel development, including combinations with ibrutinib, idelalisib, or venetoclax, and various sequences, should also be considered.

The potential benefits of collaborative trials can include a control arm that is shared among various sponsors. This would allow companies to save costs and maximize patient enrollment into trials with promising regimens, and not a control regimen (eg, single-agent chlorambucil). This design would also allow for novel–novel combinations, such as investigational monoclonal antibodies, antibody-drug conjugates combined with targeted therapies, or immunotherapy in combination with targeted therapy. With this design, there would be potential to partner early with the FDA on an approval platform, and route to phase 3 trials, as was done with the I-SPY2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2) trial.[11]

In addition, within the design, the probability of success could be modeled on an ongoing basis to determine early futility within population subsets, or success and graduation to a phase 3 trial. At present, this trial design is generally limited to phase 2 clinical trials, and phase 3 trials would be designed as traditional, randomized controlled trials. These trials are complex to design and to operate, and require experienced resources to navigate from the concept stage to execution to study completion.

Although the most mature data for ibrutinib and idelalisib show prolonged periods of PFS and OS, the majority of completed trials had relatively small sample sizes. As additional data are collected on these and on forth-

coming targeted agents, comparisons to imatinib in CML may become a reality, and would potentially show durable benefit for select patient subsets. In the future, the goals of therapy and objectives in clinical trials will become more rigorous and include minimal residual disease–negative remission, minimal residual disease at selected time points, and durable response.

With optimal sequencing and combination therapy, cure may become the goal in select patients. Patients may soon be able to manage their CLL as a chronic condition, for prolonged periods, with ≥1 orally dosed medications rather than traditional cytotoxic chemotherapy. Some patients may be able to live a normal life span, with a good quality of life. Although this would indicate significant improvement for patients with CLL, it may also necessitate the development of other BTK/PI3K-delta inhibitors for the second- and third-line setting, to combat resistance mechanisms. Further research into these resistance mechanisms will be needed, as well as good companion diagnostics.

Another result likely to manifest from the greatly improved outcomes attained with newer therapies is a decrease in the number of patients with relapsed or refractory CLL who may be available for clinical trial enrollment, which would increase the competition for patients. Enrollment is already a challenge, and if more patients have long-lasting durable response to first-line treatment, then the pool of potential candidates with relapsed or refractory CLL for clinical trials would decrease even further. Furthermore, the small proportion of tumors that do progress on these newly approved first-line regimens are likely to have poor cytogenetic markers, and may develop Richter transformations, disqualifying them from enrollment in a CLL trial. Because of these challenges, collaborative and adaptive trial designs will become increasingly necessary to continue studies and development of CLL therapies. ■

Author Disclosure Statement

Dr Combest, Dr McAtee, and Dr Reitsma are employees of Pharmaceutical Product Development (PPD), Wilmington, NC. Dr Danford is a Research Fellow at PPD. Dr Andrews and Dr Simmons have no relevant disclosures to report.

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