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%. 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.

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-\(\gamma\) through phosphorylation, which mobilizes internal calcium and activates the NF-\(\kappa\)B 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.

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-
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 costs, 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).

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. In certain Asian countries (eg, China, India, and Japan), the percentage of CLL cases is much lower (4%-10% of leukemias). 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. The incidence of CLL is approximately 4.2 cases per 100,000 people in the Western world. The global CLL incidence and 3-year prevalence are shown in the Figure. 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 Reitsera 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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