Ibrutinib, Obinutuzumab, Idelalisib, and Beyond: Review of Novel and Evolving Therapies for Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL) is a neoplasm resulting from the progressive accumulation of functionally incompetent monoclonal B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. It is the most common leukemia in Western countries and typically occurs in elderly patients. Initial treatment of CLL often includes a first-generation anti-CD20 antibody (rituximab) with chemotherapy and is the current standard of treatment for "younger" old adults (< 70 yrs of age) or older, clinically fit patients. However, because disease progression and drug resistance are inevitable, patients typically die from their disease or treatment-related complications. Improved understanding of the B-cell receptor signaling pathway, which is essential for normal B-cell growth and tumorigenesis, has led to the development of targeted therapies, with improved short-term clinical outcomes. Ibrutinib, obinutuzumab, and idelalisib, three novel agents recently approved by the U.S. Food and Administration for CLL, all have the potential to change the treatment paradigm. In this article, we describe the pathogenesis of CLL and some of its prognostic factors. Emphasis is on the pharmacology, dosing, clinical efficacy, safety, and place of therapy of ibrutinib, obinutuzumab, and idelalisib. Investigational agents that target different parts of the CLL pathogenic pathway are also described.

KEY WORDS B-cell receptor, bruton tyrosine kinase, chemoimmunotherapy, chronic lymphocytic leukemia, ibrutinib, idelalisib, obinutuzumab, CD20, microenvironment.

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Chronic lymphocytic leukemia (CLL) is a heterogeneous B-cell neoplasm with a variable disease course that remains incurable.[1] It is the most common adult leukemia in Western countries and is uncommon in the Asian population. The median age at diagnosis is 72 years. In the United Startes, 15,680 new cases and 4580 deaths due to CLL are estimated to occur in 2014.[2] CLL is characterized by clonal proliferation and accumulation of monoclonal mature B cells in the peripheral blood, bone marrow, and lymphoid tissue (lymph nodes and spleen). These B cells express the B-cell surface antigens CD19, CD20, and CD23. The hallmark of CLL cells is the expression of CD5. Each clone of leukemia cells is restricted to express either κ or λ immunoglobulin light chains.[3, 4]

Chronic lymphocytic leukemia cells in the blood are resting cells with gene expression profile similar to the memory B cells. However, CLL cells in the lymph node and bone marrow show characteristics of activated B cells and demonstrate increased proliferation with other cells, particularly T cells and stromal cells. This striking biologic difference is due to the interaction of the CLL leukemic cells with the surrounding nonma-

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lignant cells, the "microenvironment" in the lymph node and bone marrow. Due to the influence of chemokines and cytokines produced by the stromal cells and monocyte-derived cells ("nurse-like cells"), CLL cells survive and proliferate in this microenvironment distinct from the peripheral blood.[5–7]

According to the World Health Organization (WHO),[8] CLL and small lymphocytic lymphoma (SLL) are considered different manifestations of the same disease. Patients with both diseases are often asymptomatic and are diagnosed with an incidental finding of lymphocytosis and lymphadenopathy. Some patients with CLL survive for years without therapy and eventually die from unrelated disease; others have rapid disease progression despite aggressive therapy. Thus, improving our understanding about the molecular biology and progression of CLL will help define risk stratification of patients and design potential new therapies.

During normal B-cell development, *V* genes that encode the immunoglobulin variable segments that serve as the receptor for antigens undergo somatic mutation when an antigen is engaged to the receptor. Through these mutations, the descendant B cells that harbor those antigens with enhanced antigen-binding affinity proliferate. Based on the presence or absence of acquired somatic mutations in the immunoglobulin heavy-chain variable region (IGVH), CLL can be divided into two main subgroups: those with mutation in the *IGVH* gene and those with a nonmutated *IGVH* gene. Patients with mutated *IGVH* genes are thought to have CLL cells derived from the antigen-experienced B cells with an indolent course and longer survival than patients who have nonmutated *IGVH*.[9, 10] Of note, the mutational status of CLL cells is fixed, rather than gained or lost during the course of disease. Thus, the mutational status of the *IGVH* gene provides significant prognostic information. Furthermore, molecules that modulate the B-cell antigen receptor (BCR) signaling pathway may have a prognostic role in disease outcome. Two prognostic molecular markers in the BCR pathway important to the pathogenesis of CLL are zeta chain-associated protein kinase 70kDa (ZAP-70) and CD38. Additional adverse cytogenetic abnormalities associated with CLL are increasingly used to better identify patients with an aggressive disease and predict the prognosis (Table 1).[11–14] Currently, only two genetic abnormalities (17p deletion or *TP53* gene mutation and 11q deletion) are important to determine treatment choices.[15]

Treatment Overview

The age at initial diagnosis of CLL is generally 65–72 years. Older patients with CLL often present with multiple comorbidities, which may decrease patients' ability to tolerate conventional cytotoxic chemotherapy. Current consensus-based guidelines[15, 16] suggest that there is no benefit in treating early asymptomatic patients. Treatment is recommended only for progressive, symptomatic patients. During the past 30 years, therapeutic approaches for symptomatic patients have evolved from the use of alkylating agents (such as chlorambucil, cyclophosphamide) as single agents or with prednisone to purine analog–based regimens and chemoimmunotherapy combinations. The current standard for treatment-naïve and clinically fit patients with advanced stage or progressive CLL is a chemoimmunotherapy regimen consisting of fludarabine, cyclophosphamide, and rituximab (FCR).[17] However, the FCR regimen is not able to overcome the adverse cytogenetic abnormalities of CLL such as deletion 17p or *TP53* gene mutations, both of which indicate refractoriness to chemotherapy as well as poor disease outcome.[12, 18, 19] The use of new agents with better toxicity profile and non-cross-resistance to fludarabine-based regimens is necessary to improve treatment outcomes.

Because chemoimmunotherapy is not curative and treatment options for relapsed disease tend to have increased toxicity and reduced antitumor activity, the U.S. National Comprehensive Cancer Network (NCCN) guidelines[15] recommend enrollment in clinical trials as the preferred therapy for all patients. Allogeneic hematopoietic stem cell transplantation should be offered to eligible patients. In the absence of suitable clinical trials, treatment recommendations should be based on factors such as the overall fitness of the patient (i.e., age, performance status, and presence of comorbidities), presence of high-risk genetic abnormalities (e.g., 11q deletion, 17p deletion), clinical stage, and the treatment setting (first vs second line).[15]

Thus, there is an unmet medical need for new or alternative treatments for patients who cannot tolerate or have developed resistance to conventional cytotoxic chemotherapy or chemoimmunotherapy. Ibrutinib, a small molecule inhibitor that targets the BCR pathway, and obinutuzumab, a novel anti-CD20 fully humanized

Table 1. Summary of Major Genetic Biomarkers of Prognostic Value in Chronic Lymphocytic Leukemia (CLL)

Prognostic Genetic/Molecular Biomarker	Significance/Comments
IGVH gene mutation[9–11]	Mutated *IGVH* is associated with an indolent disease course and longer survival than nonmutated IGVH Nonmutated IGVH is associated with poor prognosis and decreased survival *IGVH* gene rearrangement that involves the *V(H)3-21* gene is associated with a poor outcome regardless of the *IGVH* mutational status
CD38[10]	B-cell surface molecule that affects the proliferation and longevity of the CLL clones. It enhances and fine tunes the BCR signaling as well as regulating the apoptosis of B cells Expression of CD38 (≥ 7% of B cells) indicates a more aggressive disease course of CLL
ZAP70[10, 11]	Intracellular protein that transfers activation signals from the B-cell receptors to T cells and natural killer cells involved in the T-cell receptor signaling and is aberrantly expressed in CLL Expression of ZAP70 (≥ 20% of B cells) indicates a more aggressive disease course of CLL
Deletion of the long arm of chromosome 13[12] (del 13q)	Most common genetic abnormality (55%) Associated with a favorable prognosis and the longest median survival (133 mo)
Deletion of the long arm of chromosome 11[12] (del 11q)	Occurs in 18% of patients Associated with extensive lymphadenopathy, disease progression, and shorter median survival (79 mo)
Deletion of the short arm of chromosome 17[12] (del 17p) or *TP53* (a tumor suppressor gene) mutation	Occurs in 7% of patients Associated with the worst prognosis and poor response to chemotherapy, with median overall survival of only 32 mo *TP53* gene mutation is predictive for resistance to chemotherapy and prognostic for poor survival regardless of 17p chromosome status
NOTCH1, *SF3B1*, *BIRC3* gene mutations[13, 14]	Emerging genetic biomarkers associated with poor prognosis for CLL

monoclonal antibody, have recently received FDA approval for the treatment of CLL. These novel agents target the signaling pathways that are hyperactivated in CLL with low rates of adverse drug effects. Despite the low frequency of high-risk genetic abnormalities (e.g., 17p deletion, 11q deletion, nonmutated *IgVH*) in the clinical trials, these novel agents appeared effective even in patients with chromosomal abnormalities and adverse prognostic factors.[19]

Ibrutinib

In February 2014, ibrutinib (Imbruvica, Pharmacyclics, Inc., Sunnyvale, CA, and Janssen, Horsham, PA) received FDA accelerated approval for an expanded indication in CLL patients who have received at least one prior therapy. It had previously been approved in November 2013 for the treatment of mantle cell lymphoma. In June 2014, ibrutinib received breakthrough therapy designation and approval for patients with CLL who carry a deletion in chromosome 17 (17p deletion).

Pharmacology and Pharmokinetics

B-cell receptor serves as the receptor for antigens. It is a transmembrane protein composed of immunoglobulin chains. The BCR signaling pathway is involved in the differentiation, proliferation, apoptosis, and other cellular processes for normal B-cell development and survival (Figure 1).[20] It is also implicated in the pathogenesis of several B-cell malignancies, such as diffused large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, CLL, and SLL.[21–25]

Bruton tyrosine kinase (BTK) is a member of the Tec kinase family that is essential for BCR signaling.[25] BTK is expressed in B cells and myeloid cells but not in plasma cells or T cells. It is positioned early in the BCR signaling pathway, with proximity to two nonreceptor (i.e., cytoplasmic) tyrosine kinases, namely spleen tyrosine kinase (SYK) and the delta (δ) isoform of phosphoinositide 3-kinase (PI3K). Notably, two types of signals emanate from the BCR: a "tonic" survival signal and an antigen-induced activation signal. The "tonic" survival signal, mediated by

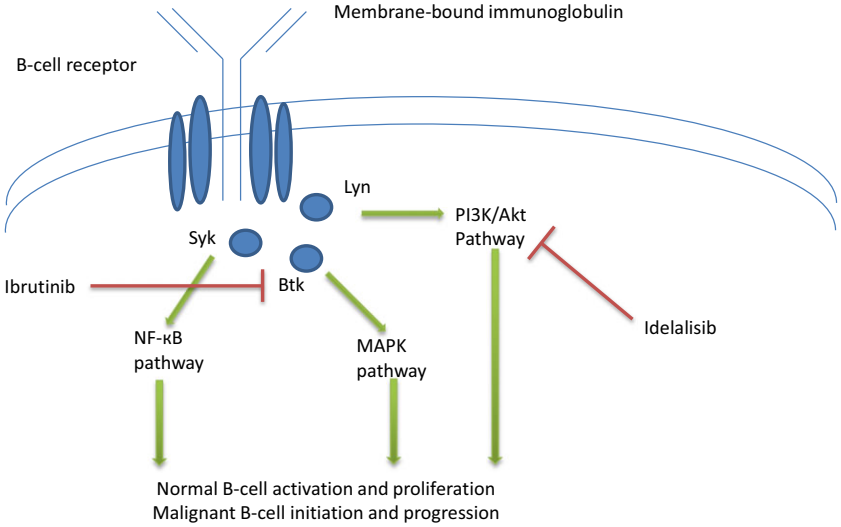

Figure 1. B-cell receptor signaling and its targeting by small molecule inhibitors. Antigen binding to the B-cell receptor (BCR) induces phosphorylation by the tyrosine kinases LYN and SYK. SYK activates phosphoinositide 3-kinase (PIP3Kδ), which converts phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 is the docking site for the cytoplasmic kinases Bruton tyrosine kinase (BTK) and AKT. BTK phosphorylates and activates phospholipase Cγ2 (PLCγ2), which generates second messengers to activate other signaling molecules, leading to the activation of nuclear factor-κ B (NF-κ B) that regulate the gene expression of several survival factors. Ibrutinib inhibits the BTK enzyme, whereas idelalisib inhibits the PIP3Kδ enzyme. Both inhibitory mechanisms lead to decreased malignant B-cell survival.

the PI3Kδ enzyme, is independent of antigen and is important for the development and survival of all mature B cells. On the other hand, antigen-induced BCR signaling activates several tyrosine kinases in addition to PI3Kδ to promote cell growth, proliferation, maturation, and survival. On antigen binding, the activated BCR activates SYK and lck/yes novel tyrosine kinase (LYN), which in turn activate the signaling pathway that involves additional kinases, adaptor molecules, and the generation of second messengers. Activated BTK and PI3Kδ further activate downstream kinases such as protein kinase B (AKT), mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK), which are involved in cellular processes such as apoptosis, cell proliferation, transcription, and cell migration of the B cells.[20–22]

Ongoing antigen-dependent BCR signaling may contribute to CLL pathogenesis through the activation of BCR and nuclear factor (NF)-κ B pathways in the lymph nodes. For instance, chronic stimulation of B cells by microbial or viral antigens is known to cause oncogenesis in some lymphomas, notably the mucosa-associated lymphoid tissue lymphoma and the marginal zone lymphoma, that arise in response to infections with *Helicobacter pylori* and hepatitis C virus, respectively.[25, 26]

Ibrutinib is a small molecule inhibitor of the BTK enzyme. It forms a covalent bond with the cysteine-481 residue of the enzyme, leading to irreversible enzyme inhibition at the nanomolecular concentration.[27] In preclinical studies,[28–30] ibrutinib was shown to be proapoptotic and antiproliferative and inhibited the migration and adhesion of the malignant CLL cells to the tumor microenvironment. By inhibiting the BCR, ibrutinib inhibits the growth and survival of the malignant CLL cells. Interestingly, ibrutinib may play a role in T-cell signaling.[31, 32]

Ibrutinib is rapidly absorbed after oral administration. Systemic exposure is proportional with doses up to 840 mg.[33] In a phase I trial,[34] the maximum tolerated dose was not reached when ibrutinib was given once/day. The maximum plasma concentration (C_{max}) is reached in 1–2 hours. Steady state was reached at a dosage of 560 mg once/day with apparent volume of distribution (V_d) of 10,000 L, indicating significant body distribution. Administration with food increased the systemic exposure by ~2-fold. Thus, it is recommended that ibrutinib be taken without food once/day.[33]

Ibrutinib is metabolized by the cytochrome P450 (CYP) 3A enzymes and to a lesser extent by the CYP2D6 enzyme. Strong CYP3A inhibitors such as ketoconazole increased the maxi-

mum concentration and exposure (area under the concentration–time curve) of ibrutinib by 29- and 24-fold, respectively.[27] The prescribing information recommends against coadministration with moderate or strong CYP3A inhibitors. If avoidance of coadministration is not feasible, the dosage of ibrutinib must be reduced (Table 2). Conversely, coadministration with a strong CYP3A4 inducer (e.g., rifampin) must be avoided due to the decreased concentration of ibrutinib.[33] Drug clearance is not altered by age (37–84 yrs) or gender. Its systemic exposure is increased 6-fold in patients with moderate hepatic impairment. Currently, there is no guideline available on dose adjustment in patients with hepatic or renal impairment. It is not cleared significantly by the kidneys.[33]

Clinical Trial Experience

In a phase I study,[34] highly specific fluorescent probes that bind to the BTK enzymes were used to measure the enzyme occupancy, which has been shown to correlate with the blocking of the BCR signaling and the optimal biological dose of the BTK inhibitor.[27] A fixed daily dose of 560 mg (or 8.3 mg/kg; average weight 70 kg) led to full enzyme occupancy in a range of different body weights, appeared to be tolerated, and was selected as the dose for subsequent phase II studies.

In a phase Ib/II multicenter study,[35] single-agent ibrutinib was studied in 85 patients with refractory of relapsed CLL. Patients received either 420 mg once/day (n=51) or 840 mg once/day (n=34). Among the 51 patients, 3 patients had SLL. The primary end point was the safety of the two fixed-dose regimens. The secondary points were overall response rate, progression-free survival, pharmacodynamics, and pharmacokinetics. Results showed that the overall response rate was 71%, with the majority of the responses being partial responses (68%). The study indicated that once-daily dosing of ibrutinib at 420 mg or 840 mg provided effective and complete occupancy of BTK, a surrogate marker for the enzyme inhibition. Because both doses were considered equally efficacious, the lower dose of 420 mg was chosen as the initial dose for CLL.

In addition, responses were also seen in patients who had received prior purine-based analog and chemoimmunotherapy and those with 17p deletion. At 26 months, the estimated progression-free survival was 75% and the overall survival was 83%. Adverse effects were mostly grades 1–2 (according to the National Cancer Institute's Common Terminology Criteria for Adverse Effects) and included transient diarrhea, fatigue, and upper respiratory infections. This study demonstrated that ibrutinib is a favorable option for relapsed or refractory CLL with high-risk genetic lesions.[28] However, because these trials enrolled only a small number of patients, differences between clinical outcome and adverse prognostic factors such as age, number of prior lines of treatment, and abnormal cytogenetics may not have been observed.

Interestingly, ibrutinib caused transient lymphocytosis that was concurrent with the decrease in lymphadenopathy and/or spleen size. Continued treatment led to the resolution of the asymptomatic lymphocytosis. This suggested that lymphocytosis was not a sign of progressive disease but rather signified the egress of CLL cells from the microenvironment.[29]

Table 2. Recommendations for Dosage Adjustment and Modification of Ibrutinib-Induced Toxicities[33]

Toxicity	Dosage Adjustment and Modification
Concomitant strong CYP3A inhibitors	Consider administering 3A4 inhibitor for 7 days or less. Use of strong 3A4 inhibitor is not recommended for chronic use of ibrutinib. Consider interrupting ibrutinib therapy until the 3A4 inhibitor is no longer necessary.
Concomitant moderate CYP3A inhibitors	Reduce ibrutinib dosage to 140 mg/day.
Neutropenia with fever or infection (grade 3[a, c] or higher)	Interrupt ibrutinib therapy, and resume at the starting dose when toxicity resolves or is at grade 1 level.
Grade 4[a, b] hematologic toxicity	If grade 4 toxicity recurs, reduce dosage by 140 mg/day (e.g., 420 to 280 mg/day).
Nonhematologic toxicity (grade 3[c] or higher)	If grade 4 toxicity recurs the third time, further reduce dosage by 140 mg/day (e.g., 280 to 140 mg/day). If toxicities persist after two reductions, discontinue ibrutinib.

[a]Grade based on Common Terminology Criteria for Adverse Effects from the National Cancer Institute (Version 4.0).
[b]Grade 4 hematologic toxicity: absolute neutrophils count < 0.5×10^9/L, platelets < 25×10^9/L, hemoglobin < 6.5 g/L.
[c]Grade 3 neutropenia: absolute neutrophils count < $1.0–0.5 \times 10^9$/L.

The benefit-versus-risk profile of ibrutinib as frontline therapy in treatment-naïve patients was recently evaluated in a phase Ib/II study.[36] Thirty-one patients who were at least 65 years old (median age 71 yrs, range 65–84 yrs) with symptomatic CLL (n=29) or SLL (n=2) were enrolled. Patients received ibrutinib 420 mg (three 140-mg capsules) orally once/day or 840 mg (six 140-mg capsules) orally once/day in a 28-day cycle until disease progression or intolerable toxicity. The primary end point was the safety of the fixed dose, assessed by the frequency and severity of the adverse events. The secondary end points were overall response rate, progression-free survival, long-term tolerability, and pharmacodynamics. Of the 31 patients, 22 (71%) achieved an overall response; 4 (13%) patients had a complete response. Ibrutinib-induced lymphocytosis occurred in 17 (55%) of 31 patients, with the effect peaking at a median of 1.1 weeks (range 1.1–3.9 wks) followed by a slow decline. Lymphocytosis was concomitant with reduction in lymph node size. Median (range 1.8–4.6 mo) time to initial response was 1.9 months. Overall survival was 96.6% (95% CI 77.9–99.5%) and there was no difference by dose. BTK occupancy was more than 90% in both arms. The most common adverse event was diarrhea, which was self-limiting and often resolved without discontinuation of the therapy. Other common adverse events included nausea, fatigue, and hypertension. There was no difference in the safety profile of patients who received ibrutinib either 420 mg or 840 mg once/day. However, no definitive conclusion can be made because of the uneven distribution of patients in these two arms.[36]

Dosing

The FDA-approved starting dose of ibrutinib is 420 mg orally once/day and suggested dose reductions for toxicities are provided in the prescribing information (Table 2).

Safety

The majority of adverse events reported were grade 1 or 2. Most common adverse events (> 20% of patients) were diarrhea, upper respiratory tract infection, fatigue, cough, arthralgia, rash, pyrexia, and peripheral edema.[36, 37] In a phase I follow-up study, patients continued treatment for 1 year or longer; the rate of serious adverse events was 43% in the first year of treatment and 32% after the first year. Within the first year of treatment, 12 (8%) patients discontinued therapy, while 6 patients (6%) discontinued therapy after the first year. The most frequent grade 3 or greater adverse events were pneumonia, hypertension, neutropenia, thrombocytopenia, and diarrhea.[39]

Ibrutinib exhibits antithrombotic properties and is associated with ecchymosis or contusion but is rarely associated with serious bleeding in patients taking oral anticoagulants. Researchers hypothesized that ibrutinib may potentiate bleeding by inhibiting the BTK enzyme, which is a key component in the signaling of glycoprotein receptors, as well as by disrupting platelet adhesion and aggregation.[38] The prescribing information recommends holding ibrutinib for 3–7 days before and after surgery to mitigate the risk of perioperative bleeding (Table 2).[33]

Ibrutinib is classified as a pregnancy category D agent. Animal studies suggest that ibrutinib may cause reduced fetal weight. If a woman plans to take this medication during pregnancy or if a woman becomes pregnant while taking this medication, she should be apprised of the potential hazard to the fetus.[33]

Place in Therapy

Ibrutinib is associated with demonstrated improvement in overall response and overall survival as frontline therapy for treatment-naïve patients and as a salvage therapy in relapsed or refractory CLL. Among patients with relapsed or refractory CLL, the response rate is ~71% and a progression-free survival rate of 75% at 2 years. The optimal length of treatment remains to be established. With the significant improvement in responses in heavily pretreated patients, ibrutinib has filled the unmet medical need of many patients with relapsed or refractory CLL who cannot tolerate systemic cytotoxic chemotherapy and/or are not eligible for hematopoietic stem cell transplantation.

Nevertheless, the long-term safety for ibrutinib has not been established. Caution must be exercised for the development of resistant clones due to the persistence of the disease, because most patients treated with iburtinib often have prolonged partial remissions. Moreover, about 2–5% of CLL patients will develop Richter's syndrome or transformation (transformation from CLL into an aggressive B-cell lymphoma such as diffuse large B-cell lymphoma) during the disease course

and treatment.[39] The incidence of transformation increases with the number of prior chemotherapy regimens. This risk has not been fully investigated because most ibrutinib trials to date for relapsed CLL were relatively small. At present, it remains unknown how relapsed CLL patients can be best salvaged. Current NCCN guidelines[15] recommend ibrutinib as the most preferred agent in the treatment of refractory/relapsed CLL without 11q and 17p deletions for patients older than 70 years or those younger than 70 years without significant comorbidities followed by chemoimmunotherapy.

A clinical trial is currently under way to investigate ibrutinib compared with chlorambucil in previously untreated patients with CLL.[40] In addition, a phase Ib/II trial is investigating the combination of ibrutinib with the bendamustine-rituximab (BR) regimen versus BR alone in patients with relapsed/refractory CLL.[41] Together, these trials are likely to shed light on the role of ibrutinib with conventional chemoimmunotherapy or other treatment options.

Obinutuzumab

Obinutuzumab (Gazyva, Genentech Inc., South San Francisco, CA) was approved by the FDA in November 2013 in combination with chlorambucil for patients with previously untreated CLL.

Pharmacology and Pharmacokinetics

Obinutuzumab is a fully humanized, type II anti-CD20 glycoengineered, third-generation monoclonal antibody. Type I anti-CD20 antibodies such as rituximab (first generation) and ofatumumab (second generation) require a cross-linking antibody to induce direct apoptosis.[42, 43] In comparison, type II anti-CD20 antibodies, such as obinutuzumab, induce apoptosis without a cross-linking antibody.[44] And unlike the type I anti-CD20 monoclonal antibodies, the type II anti-CD20 monoclonal antibodies do not segregate the CD20 molecules into the lipid raft (a local domain in the phospholipid bilayer). Instead, they activate lysosomal-dependent apoptosis, which depends on homotypic adhesion (the attachment of a cell to a second cell of the identical type via adhesion molecules). By inducing homotypic adhesion, obinutuzumab is postulated to cause a higher degree of direct cell death than antibody-dependent cellular cytotoxicity.[20, 45]

Additionally, obinutuzumab has been "glycoengineered" through the reduction of fucose residues in the Fc (Fragment, crystallizable) portion of the antibody, allowing stronger binding affinity with various effector cells. Consequently, there is a greater degree of antibody-dependent cellular cytotoxicity. Furthermore, in vitro studies have shown that obinutuzumab also targets CD16 to activate the polymorphonuclear neutrophils to induce phagocytosis.[46]

The GAUGUIN study[47] was a multicenter, open-label, randomized, phase II trial that examined the safety and efficacy of two different doses of obinutuzumab in patients with diffuse large B-cell lymphoma and mantle cell lymphoma. Pharmacokinetic analysis showed that the higher-dose group of 1600 mg/800 mg achieved steady-state concentrations, while the lower dose group of 400 mg/400 mg did not. The GAUDI study[48] was a phase Ib study that compared the same two doses of obinutuzumab, using standard backbone regimens of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for 6–8 cycles and fludarabine with cyclophosphamide (FC) for 4–6 cycles. There were 56 patients with relapsed or refractory follicular lymphoma included in the study. In both trials, pharmacokinetic studies showed that the 1600 mg/800 mg dose of obinutuzumab achieved and maintained higher concentrations throughout the treatment cycles.

The geometric mean volume of distribution of obinutuzumab is approximately 3.8 L from the population analysis.[49] The drug is eliminated via a linear clearance pathway and a time-dependent, nonlinear clearance pathway. The impact of the latter pathway diminishes following the continuation of drug therapy, suggesting target-mediated drug disposition. The clearance and half-life are ~0.09 L/day and ~28.4 days, respectively. Body weight was associated with changes in drug exposures but did not warrant dose modification. Mild or moderate renal impairment (creatinine clearance > 30 ml/min) did not affect drug exposure. Dose adjustment is not necessary for patients with severe renal (creatinine clearance < 30 ml/min) or hepatic impairment because the drug is catabolized by ubiquitous proteolytic enzymes. In addition, obinutuzumab is a pregnancy category C agent. Women of childbearing potential should use effective contraception while receiving the medication and for 12 months after treatment.[49]

Clinical Trial Experience

One large multinational, open-label, randomized, phase III trial evaluated obinutuzumab with chlorambucil in patients with CLL and multiple comorbidities.[50] The study stratified 781 patients in a 1:2:2 ratio to receive chlorambucil monotherapy, rituximab plus chlorambucil, or obinutuzumab plus chlorambucil, respectively. Chlorambucil was administered at a dose of 0.5 mg/kg on days 1 and 15 of each cycle. Rituximab was dosed intravenously as 375 mg/m^2 on day 1 of the first cycle and as 500 mg/m^2 on day 1 of cycles 2–6. Obinutuzumab was given intravenously at a dose of 1000 mg on days 1, 8, and 15. This was later amended in the study protocol such that the first dose was administered over 2 days in 100- and 900-mg doses on days 1 and 2, respectively. This dose was determined by previous researchers[47] to be a more practical schedule than the 1600 mg/800 mg dose in previous phase I/II studies,[51] and would still give rise to steady-state concentrations. For each arm, a total of six cycles were given.

The primary end point was progression-free survival. Patients enrolled in the study had a median age of 72 years, with approximately 60% of patients having a Binet stage of A or B and a nonmutated *IgVH* gene. Additionally, 82% of patients enrolled had more than three comorbidities. Efficacy results showed that either obinutuzumab or rituximab with chlorambucil increased median progression-free survival compared with chlorambucil alone. Specifically, obinutuzumab with chlorambucil had a statistically significant median progression-free survival of 26.7 months versus 11.1 months with chlorambucil alone (hazard ratio [HR] 0.18, 95% CI 0.13–0.24; $p<0.001$). Results showed that the rituximab-chlorambucil combination had a median progression-free survival of 16.3 months, which was also statistically significant compared with the chlorambucil monotherapy (HR 0.44, 95% CI 0.34–0.57; $p<0.001$). In the second phase of the study, obinutuzumab plus chlorambucil was compared with rituximab plus chlorambucil for overall, complete, and partial responses. A total of 333 patients in the obinutuzumab-plus-chlorambucil group and 329 patients in the rituximab-plus-chlorambucil group were evaluated. Analysis showed that obinutuzumab with chlorambucil achieved statistically significant greater overall and complete response rates than did rituximab with chlorambucil (Table 3).[50]

Infusion-related reactions, neutropenia, and thrombocytopenia were the most common adverse events in the obinutuzumab-plus-chlorambucil group. The most common grade 3 and 4 adverse event obinutuzumab was neutropenia. There were two deaths in the obinutuzumab-plus-chlorambucil group due to hemorrhagic stroke and plasma cell myeloma, one death in the rituximab-plus-chlorambucil group due to cardiac arrest, and three deaths in the chlorambucil monotherapy group, which were attributed to intracranial hemorrhage, respiratory failure, and infection.[50]

Of note, the obinutuzumab-plus-chlorambucil combination was associated with more severe adverse events overall (70% vs 55%), more infusion-related reactions (20% vs 4%), and thrombocytopenia (10% vs 3%) compared with the rituximab-plus-chlorambucil combination. At a median follow-up of 18.7 months, obinutuzumab improved median progression-free survival (26.7 vs 15.2 mo, HR 0.39, 95% CI 0.31–0.49). Future long-term follow-up is needed to evaluate overall survival.[50]

Dosing

Obinutuzumab is administered as an intravenous infusion for six 28-day cycles. In cycle 1, 100 mg is infused on day 1, 900 mg is infused on day 2, then 1000 mg is infused on days 8 and 15. In cycles 2–6, obinutuzumab 1000 mg is infused on day 1.

For the standard 1000-mg infusion, it is recommended that the infusion be started at a rate of 100 mg/hour and increased by 100 mg/hour every 30 minutes up to a maximum rate of 400 mg/hour.

Safety

Compared with those who received chlorambucil alone, the most common grade 3 or higher adverse events noted with obinutuzumab plus chlorambucil in the CLL11 trial were neutropenia (34% vs 16%), infusion-related reactions (21% vs 0%), thrombocytopenia (11% vs 3%), and leukopenia (5% vs 0%); rates of anemia were slightly lower in the combination therapy group (4% vs 5%). The overall incidence of infusion-related reactions of any grade was 69% in obinutuzumab recipients compared with zero in those who received chlorambucil alone. Premedications such as antihistamine, acetaminophen, and steroids are necessary to decrease the risk of

Table 3. Summary of Key Clinical Trials of Ibrutinib, Obinutuzumab, and Idelalisib for Chronic Lymphocytic Leukemia

Trial	Study Setting/Adverse Patient Characteristics	Dosing Schedule/Clinical Efficacy	Major Adverse Effects
Advani et al[34]	Relapsed or refractory setting	Pts (n=56) received escalating doses (1.25, 2.5, 5, 8.3, or 12.5 mg/kg/day) of ibrutinib. Two schedules were evaluated: (1) 28 days on, 7 days off, (2) once-daily continuous dosing. Dose escalation proceeded until the MTD or until three dose levels above full enzyme occupancy by ibrutinib.	Mostly grade 1 and 2 in severity and self-limited. No evidence of cumulative hematologic and nonhematologic risk with prolonged dosing
	Phase I, open-label, multicenter, dose-escalation trial of ibrutinib	Full occupancy of the BTK enzyme occurred at 2.5 mg/kg/day, and dose escalation continued to 12.5 mg/kg/day without reaching MTD.	
	Pts had failed at least one prior therapy	ORR 60% (in 50 evaluable pts) ORR 54%, CR 16% Median PFS 13.6 mo	Grade 3 or 4 hematologic toxicities: neutropenia (12.5%), thrombocytopenia (7.2%), anemia (7.1%)
Byrd et al[35]	Relapsed/refractory disease	Pts (n=85) received ibrutinib p.o. once/day. Among them, 51 received 420 mg/day and 34 received 840 mg/day.	Mostly grade 1 or 2 toxic effects that included transient diarrhea (42%, all grades), fatigue (27%, all grades), URI (28%, all grades)
	Phase Ib/II, multicenter Pts had received at least two previous therapies (including a purine analog). Another cohort was refractory to chemoimmunotherapy	n=85 ORR 71% PR 68% PFS at 26 mo 75% (estimated) OS 83% Outcome was independent of clinical and genetic risk factors and advanced disease	Minimal hematologic toxicity with extended treatment
O'Brien et al[36] (NCT01105247 trial)	Treatment naïve	Pts (n=29) received 28-day cycles of once-daily ibrutinib 420 mg or ibrutinib 840 mg. The 840-mg dose was discontinued after enrollment due to reported efficacy of 420 mg	55% drug-induced lymphocytosis
	Phase Ib/II, open-label, multicenter 74% age ≥ 70 yrs del 17p 6% del 11q 3% del 13q 55%	ORR 71% CR 13% PR 55% Nodular PR 3% Median time to initial response 1.9 mo OS 96.6% (no difference between 420 vs 840 mg/day p.o.)	Adverse effects > 20% (all grades): diarrhea (68%), nausea (48%), fatigue (32%), nausea (48%), hypertension (29%), peripheral edema (29%), URI (26%), UTI (23%) vomiting (23%), arthralgia (23%) Seven grade 5 reactions reported: pneumonia, infiltrating-like pneumonia, cryptococcal pneumonia, CLL, Richter's transformation, sarcoma, SIRS

(continued)

Table 3. (continued)

Trial	Study Setting/Adverse Patient Characteristics	Dosing Schedule/Clinical Efficacy	Major Adverse Effects
Byrd et al[56] (RESONATE trial or NCT 01578707 trial)	Relapsed or refractory setting	Pts (n=391) randomly assigned to either ibrutinib 420 mg once/day p.o. until disease progression/intolerable toxicity or ofatumumab intravenously (initial dose of 300 mg at week 1, followed by 2000 mg weekly for 7 wks and then every 4 wks for 16 wks) for up to 24 wks. Crossover to ibrutinib in the ofatumumab arm was allowed due to promising result of ibrutinib	Grade 3 or greater events that occurred more frequently in the ibrutinib group than ofatumumab group: diarrhea (4% vs 2%), atrial fibrillation (3% vs 0%)
	Phase III, randomized, open-label, multicenter	Ibrutinib significantly prolonged rate of OS(HR for death in the ibrutinib group 0.43 (95% CI 0.24–0.79, p=0.005)	
	82% of patients had more than three comorbidities	OS at 12 mo: 90% in the ibrutinib group vs 81% in the ofatumumab group	Bleeding-related events of any grade were more common in the ibrutinib group than in the ofatumumab group (44% vs 12%)
		ORR was significantly higher in the ibrutinib group than in the ofatumumab group (42.6% vs 4.1%, p<0.001)	Common adverse events in pts receiving ibrutinib vs ofatumumab included rash (8% vs 4%), pyrexia (24% vs 15%), blurred vision (10% vs 3%). Incidence of cataracts was 3% vs 1%, respectively. Infusion-related reactions, peripheral neuropathy, urticaria, night sweats, and pruritus were more common in the ofatumumab group
Goede et al[50] (CLL11 trial)	Treatment naïve (previously untreated)	Pts (n=781) were randomized 1:2:2 to receive (1) chlorambucil (0.5 mg/kg p.o. days 1 and 15 of each cycle), (2) obinutuzumab (1000 mg intravenously on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2–6) plus chlorambucil, or (3) rituximab (375 mg/m^2 i.v. on day 1 of cycle 1, then 500 mg/m^2 on day 1 of cycles 2–6) plus chlorambucil in six 28-day cycles. Obinutuzumab-chlorambucil (n=333) or rituximab-chlorambucil (n=329), vs chlorambucil increased response rates ORR 78.4% (CR 20.7%, PP 57.7%) Median PFS 23 mo (26.7 vs 11.1 mo, p<0.001) PFS was 16.3 mo with rituximab-chlorambucil vs 11.1 mo with chlorambucil alone (p<0.001).	10% (all grades): infusion-related reaction (69%), neutropenia (40%), thrombocytopenia (15%), anemia (12%), pyrexia (10%), cough (10%)
	Phase III	ORR 65.1% (CR 7%, PR 58.1%)	
	Median age of 73 yrs, creatinine clearance of 62 ml/min and CIRS score of 8 at baseline		Infusion-related reactions and neutropenia were more common with obinutuzumab-chlorambucil than with rituximab-chlorambucil, but the risk of infection was not increased Precaution for hepatitis B virus reactivation, PML, TLS

(continued)

Table 3. (continued)

Trial	Study Setting/Adverse Patient Characteristics	Dosing Schedule/Clinical Efficacy	Major Adverse Effects
Brown et al[64]	Relapsed or refractory Phase I Bulky lymphadenopathy (80%), extensive prior therapy (median five prior regimens), treatment-refractory disease (70%, refractory to rituximab, fludarabine, and other alkylating agents), nonmutated *IGVH* (91%), and del 17p and/or *TP53* mutations	Pts (n=54) were treated at six dose levels of oral idelalisib (range 50–350 mg once/day or b.i.d.) and remained on therapy as long as there is clinical benefit Nodal response 81% ORR 72% (PR 39%) Median PFS 15.8 mo Median duration of response 16.2 mo	Most commonly observed grade 3 or higher adverse events: pneumonia (20%), neutropenic fever (11%), diarrhea (6%)
O'Brien et al[66]	Treatment naïve (initial therapy) Phase II Pts ≥ 65 yrs, median age > 71 yrs del 17p in 6 pts del 11q in 13 pts	Pts (n=64) were treated with rituximab 375 mg/m^2 weekly × 8 and idelalisib 150 mg b.i.d. continuously for 48 wks (primary study). Pts completing 48 wks without progression could continue to receive idelalisib on an extension study (n=30) Median time on treatment was 16 mo (range 0.8–27.5). ORR 96% (with 4% nonevaluable) Median time to response was 1.9 mo (range 1.0–6.5) Estimated PFS 91% (at 24 mo) Six of 6 pts with del 17p responded (1 CR, 5 PR) and 3 remained on treatment for > 21 mo Of 20 pts with B symptoms at baseline, 13 (65%) were asymptomatic by 8 wks. Conclusions: Idelalisib plus rituximab is highly active, resulting in durable disease control in treatment-naïve older pts with CLL. These results support further study of idelalisib in frontline CLL	Most frequent: diarrhea, pyrexia, chills, fatigue, rash, pneumonia, and nausea Elevated ALT/AST was seen in 60% of pts

(continued)

Table 3. (continued)

Trial	Study Setting/Adverse Patient Characteristics	Dosing Schedule/Clinical Efficacy	Major Adverse Effects
Furman et al[70] (Study 116)	Relapsed setting	Pts (n=220) were randomly assigned to receive rituximab (375 mg/m^2 i.v., then 500 mg/m^2 every 2 wks × 4 doses, then every 4 wks × 3 doses for total of 8 doses) and either idelalisib (at a dose of 150 mg) or placebo b.i.d. Study was stopped early due to overwhelming efficacy. Rituximab-idelalisib vs rituximab-placebo: PFS 93% OR at 12 mo 92% (HR 0.48, p=0.02) 93% pts had 75% reduction in LAD	No overall increase in the rate of adverse events with the addition of idelalisib to rituximab, compared with placebo and rituximab Idelalisib group: five most common adverse events: pyrexia, fatigue, nausea, chills, and diarrhea Placebo group: adverse events were similar to those in the idelalisib group. Most common: infusion-related reactions, fatigue, cough, nausea, and dyspnea
	Multicenter, randomized, double-blind, placebo-controlled, phase III Pts had decreased renal function, major coexisting illnesses (CIRS ≥ 6) Prior therapies: rituximab, cyclophosphamide, and other alkylating agents	Median duration of PFS (5.7–5.9 mo) in rituximab-placebo group was similar to that of pts receiving ofatumumab	

BTK= Bruton tyrosine kinase; CLL= chronic lymphocytic leukemia; CR= complete response; CIRS = Cumulative Illness Rating Scale; LAD = lymphadenopathy; LFTs = liver function tests; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival; PML = progressive multifocal leukoencephalopathy; PR = partial response; Pts = patients; SIRS = systemic inflammatory response syndrome; TLS = tumor lysis syndrome; URI = upper respiratory tract infection; UTI = urinary tract infection.
Note: Objective response rate = PR or CR; ORR = PR + CR.

infusion reactions. The incidence and severity of infusion-related events decreased markedly after the first infusion. Prophylaxis for tumor lysis syndrome may be necessary for patients with high tumor burden, and antimicrobial prophylaxis (e.g., ciprofloxacin, fluconazole, acyclovir, or equivalent medications) is advised. Obinutuzumab carries black box warnings regarding an increased risk of hepatitis B reactivation and the risk of progressive multifocal leukoencephalopathy. All patients should be screened for hepatitis B before starting treatment. Obinutuzumab should be discontinued in patients with hepatitis B reactivation.[50]

Place in Therapy

Obinutuzumab is the third CD20-directed cytolytic antibody (after rituximab and ofatumumab) to receive FDA approval and provides a major advance in the treatment of CLL. In the CLL11 trial,[50] 81% of the patients were 65 years or older. It was one of the few randomized trials that adequately represented the typical age of the CLL population. Results showed that the combination of obinutuzumab and chlorambucil is more effective than chlorambucil alone, has an acceptable safety profile, and is an appropriate regimen for elderly patients with previously untreated CLL and comorbidities. Based on this study, the FDA approved obinutuzumab for use in combination with chlorambucil in November 2013 for the treatment of patients with previously untreated CLL. Obinutuzumab is a preferred first-line treatment option for CLL in the NCCN guidelines[15] in patients aged 70 or older with comorbidities, regardless of chromosomal abnormalities such as 11q or 17p deletions.

The roles of rituximab and other monoclonal antibodies for CLL have recently been evaluated in a meta-analysis of literature published from 1990 to 2012.[52] The review supports the use of rituximab in combination with fludarabine-cyclophosphamide (i.e., the FCR regimen) as an option for first-line treatment as well as for patients with relapsed or refractory CLL. In younger patients (age < 65 yrs), the FCR chemoimmunotherapy is superior to either fludarabine or the FC combination regimen.[17] However, FCR combination is associated with higher incidence of opportunistic infections, prolonged myelosuppression, and increased risk of secondary malignancies such as leukemia and myelodysplastic syndromes.[53] Treatment-related complications were more frequent and more severe in older patients (> 65 yrs) because of comorbidities and reduced bone marrow reserve. Currently, the FCR regimen is FDA approved only for patients with previously untreated CD20-positive CLL. As previously discussed, patients with deletion 17p or *TP53* gene mutations are also refractory to the FCR chemoimmunotherapy.

Patients with relapsed CLL often have limited treatment options because they develop resistance or experience persistent toxic effects of previous therapies. This is particularly true for elderly patients and those with coexisting illnesses. For these patients, NCCN guidelines recognize rituximab as a treatment option. Rituximab is commonly used in such patients, although it has not been approved as monotherapy. Rates of response to rituximab vary, and the duration of progression-free survival is generally short.[54] Follow-up study of the CLL11 trial will likely determine the efficacy of obinutuzumab-chlorambucil combination versus rituximab.

The current European Society of Medical Oncology clinical practice guideline[16] supports the use of a non–CD20-targeted therapy, that is, an alemtuzumab-based regimen in patients with 17p deletion, in physically nonfit individuals without 17p deletion, or as salvage therapy after allogeneic hematopoietic stem cell transplantation. Of note is that while the manufacturer of alemtuzumab withdrew this product from the U.S. market in September 2012, it remains accessible to CLL patients through a distribution program. On the other hand, ofatumumab targets an alternative CD20 epitope and was FDA approved in 2009 for the treatment of CLL refractory to fludarabine and alemtuzumab. It has an overall response rate of 58%[55] and has been recommended in international consensus guidelines as a therapeutic option for patients with previously treated CLL. Nevertheless, in a recent phase III multicenter study of ibrutinib versus ofatumumab in CLL, ibrutinib was superior to ofatumumab in terms of overall response rate (42.6% vs 4.1%, $p<0.001$), overall survival at 12 months (90% vs 81%), and reduction (78%) in risk of disease progression (HR 0.22; $p<0.001$), regardless of genetic abnormality or resistance to purine analogs.[56]

Currently, there is no information available on early treatment with obinutuzumab single agent versus chlorambucil single agent. An early clinical trial[57] suggested that the efficacy of combining chlorambucil and prednisone was compa-

rable to that of combination chemotherapy regimen cyclophosphamide, vincristine, and prednisone (CVP) and CHOP in untreated patients with advanced CLL. Chlorambucil single agent remains an appropriate option for initial, frontline therapy, particularly in light of its low cost, low toxicity, and outpatient convenience. Its disadvantages include very low response rate and toxic effects (cytopenia, myelodysplasia, secondary leukemia) after prolonged use.[16]

To summarize, the CLL11 trial established the obinutuzumab-chlorambucil combination as an initial treatment option for CLL patients and, in particular, for those with comorbidities and advanced age. Obinutuzumab is now being studied in combination with both chemotherapy and other novel agents for CLL.[58] The sequencing of various chemoimmunotherapy regimens (e.g., FCR regimen, rituximab plus other novel cytotoxic chemotherapy agents, or obinutuzumab-chlorambucil) in treatment-naïve patients remains to be elucidated.

Investigational Therapies

The following section discusses novel agents for different signaling pathways. Collectively, these investigational agents offer the promise of revolutionizing the treatment of CLL.

Idelalisib

Idelasib (CAL-101, GS-1101, 5-fluoro-3-phenyl-2-[(*S*)-1-(9*H*-purin-6-ylamino)-propyl]3*H*-quinazolin-4-one; Zydelig; Gilead Sciences, Inc., Foster City, CA) was approved by the FDA in July 2014 for the treatment of patients with relapsed CLL, in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other comorbidities. (It was an investigational agent at the time of this manuscript preparation.) Like BTK, PI3K is one of the key cytoplasmic tyrosine kinases in the BCR signaling pathway. It generates a phospholipid second messenger at the cell membrane, PIP3 [phosphatidylinositol-(3,4,5)-triphosphate], which recruits and activates multiple intracellular enzymes that are involved in the regulation of cell functions such as proliferation, survival, and migration.[59–61] Inhibition of the PI3K delta (δ) isoform has been shown to induce apoptosis of CLL cells and other B cells and reduction in CLL leukemic cell survival.[62, 63] Of note, PI3Ks are divided into three classes (I, II, III): class I has a catalytic subunit with four different isoforms (α, β, γ, and δ). The α and β isoforms are widely expressed in many tissues, whereas the γ and δ isoforms are restricted to cells of hematopoietic origin.

PI3Kδ plays a central role in normal B-cell development and function, transducing signals from the BCR and receptors for various cytokines and adhesion molecules (e.g., integrins). PI3Kδ signaling pathways are frequently hyperactive and implicated in B-cell cancers, making inhibition of PI3Kδ a promising target for the therapy of B-cell malignancies.[64, 65] Idelalisib inhibits the survival signals from the BCR or nurse-like cells and inhibits chemotaxis or migration of CLL cells.[66] Similar to patients receiving ibrutinib therapy, those receiving idelalisib exhibit transient lymphocytosis after therapy is initiated, due to the redistribution of CLL cells from the tissue to blood. Once in the peripheral circulation, the lack of prosurvival signals ultimately sensitizes CLL cells to apoptosis.

Idelalisib represents a new class of agents that target signal transduction downstream from the BCR in malignant B cells. It is the first-in-class PI3Kδ inhibitor with potent apoptotic activity against CLL leukemic cells. It has demonstrated promising clinical activity in phase I/II studies, as both single-agent and combination therapy for CLL patients.[67–69]

Idelalisib has been tested in numerous phase I studies for patients with CLL and other B-cell malignancies.[70, 71] A phase I, dose-finding study (see Table 3)[64] evaluated the safety, pharmacokinetics, pharmacodynamics, and activity of idelalisib. Patients included in the study were diagnosed primarily with CLL plus other B-cell malignancies. In this 3 + 3 dose-escalating study, the following doses were assessed: 50 mg twice/day, 100 mg twice/day, 300 mg once/day, 150 mg twice/day, 200 mg twice/day, and 350 mg twice/day. The treatment duration was 48 weeks, while the extension phase completed in April 2014. A total of 54 patients were enrolled in the study with a median age of 63 years (range 37–82 yrs), and the majority were male. The median number of prior therapies was 5 (range 2–14), and 70% of patients were refractory to their most recent therapy. Fludarabine, rituximab, and alkylating agents were the most frequently used prior therapies.

The median duration of treatment was 15 months (range 0.2–48.7 mo). Of the original 54 patients, 29 (54%) discontinued the study due to disease progression (28%), adverse events (9%), and early death due to adverse events

(6%), particularly infection. The three most common adverse events of any grade were fatigue (31.5%), diarrhea (29.6%), and pyrexia (27.8%). Serious adverse events occurred in 36 patients; these were due to complications of pneumonia (22.2%), neutropenic fever (11.1%), and colitis (5.6%).[64]

Pharmacokinetic studies indicated that steady-state levels were reached within 8 days of continuous daily administration of idelalisib. Doses above 150 mg twice/day did not significantly improve the area under the AUC. Additionally, twice-daily dosing achieved greater plasma concentrations than once-daily dosing (451 vs 153 ng/ml). Pharmacodynamic studies showed that inhibition of PI3Kδ with idelalisib resulted in significant and persistent reduction in Akt activation, leading to normal B-cell signaling.[64]

Idelalisib single-agent therapy resulted in an overall response rate of 72%. The median time to response was 1 month (range not available), and the median duration of response was 16.2 months (range not available). Median progression-free survival was 15.8 months (range not available). Notably, patients who received doses greater than 150 mg twice/day had a median (range not available) progression-free survival of 32 months compared with those who received lower doses and had a median progression-free survival of 7 months. Overall survival was not reached in 75% of patients surviving at 36 months. In summary, this study demonstrated that idelalisib provided a favorable side effect profile with rapid inhibition of B-cell signaling, ultimately leading to improved outcomes for CLL patients.[70]

In a phase II study,[66] idelalisib 150 mg twice/day was given with 8 weekly doses of rituximab 375 mg/m^2 for 48 weeks in 64 patients with treatment-naïve CLL. The median duration of treatment with idelalisib was 16 months (range not available), and the overall response rate was 97%; 19% of patients had achieved complete response. Median progression-free survival at 24 months was estimated at 93%. Diarrhea and pneumonia occurred in greater than 10% of patients receiving idelalisib, and elevations in liver enzymes and neutropenia were the most common laboratory abnormalities.

Study 116[70] was a multicenter, randomized, double-blind, placebo-controlled, phase III trial that evaluated the use of combination rituximab and idelalisib in patients with relapsed CLL. All 220 patients received an initial 375 mg/m^2 dose of rituximab, followed by 500 mg/m^2 every 2 weeks for 4 doses, then every 4 weeks for 3 doses. Intervention groups were given either idelalisib 150 mg orally twice/day or placebo twice/day. Other inclusion criteria were a Cumulative Illness Rating Scale (CIRS; an assessment that measures functional and comorbidity status, with higher score indicating an increased severity of coexisting illness) score of 6 or greater and previous treatment with either an anti-CD20–based immunotherapy or two prior therapies. The primary end point was progression-free survival, while secondary end points were overall and complete response rates, lymph-node response, and overall survival.[70]

Enrolled patients had a median age of 71 years (range 48–90 yrs), 85% of patients had a CIRS score greater than 6, and 40% of patients had renal impairment. Patients received a median of three prior agents (range 1–12) that generally included rituximab, cyclophosphamide, and other alkylating agents.[70]

The median duration of idelalisib therapy was 3.8 months (range 1.9–8.6 mo), and 81% of patients in the idelalisib group were still receiving the drug at the time of study conclusion. Progression-free survival for idelalisib and placebo were 93% and 46%, respectively (adjusted HR 0.15, 95% CI 0.08–0.28; $p<0.001$). All secondary end points favored the use of idelalisib over placebo. The overall rate of survival for idelalisib was 92% versus 80% for placebo at the end of 12 months (adjusted HR 0.28, 95% CI 0.09–0.86; $p=0.02$). Of the original 220 patients, 176 were evaluated. All responses were partial; the rate for idelalisib was 81% and for placebo, 13% (odds ratio 29.92; $p<0.001$). The proportion of patients with greater than 50% reduction in lymphadenopathy was 93% versus 4% for placebo.[70]

Safety analysis showed that the five most common (> 20%) adverse events were pyrexia, fatigue, nausea, chills, and diarrhea. In the idelalisib group, these adverse events occurred at a rate greater than 20%. Serious adverse events were pneumonia, pyrexia, and febrile neutropenia, all of which were graded as either 1 or 2 using the Common Terminology Criteria. In addition, the most common laboratory abnormality was an elevation in liver transaminases (35%), while the most common grade 3 or higher adverse effect was neutropenia (34%).[70]

B-cell receptor signaling results in B-cell survival and growth. As cells progress through the cell cycle, they depend on cyclin-dependent kinases (CDKs) and various cyclins to advance through DNA replication, mitosis, and growth. CDKs are a novel class of agents with unique

clinical activity that has attracted attention in CLL therapy. Inhibition of CDK-7 and CDK-9[71] and concurrent decreased expression of antiapoptotic proteins led to the hypothesis that inhibition of DNA transcription may be a feasible mechanism for CLL therapy. Because NF-κ B (a protein complex that regulates transcription of DNA) is involved in many transcriptional processes, disruption of the NF-κ B pathway by CDK inhibitors is a potential target for antileukemic therapy.[71]

Dinaciclib (SCH727965) is an investigational agent that targets the cell cycle. It has nonselective activity in CLL cells.[72] In preclinical trials, it showed activity in CLL regardless of cytogenetics.[73, 74] In a phase I cohort study,[75] dinaciclib was given as five dose cohorts (5, 7, 10, 14 and 17 mg/m^2) to 33 patients with relapsed/refractory CLL. The starting dose was based on the significant CLL cell kill in preclinical assays. Results showed that the median number of prior therapies was 4 (range 1–12), and the median number of treatment cycles received was 5 (range 1–16). Partial response was observed in 15 (45%) patients, including many who had undergone prior fludarabine-based therapies and those with 17p deletion. Pharmacokinetic analysis showed that dinaciclib is rapidly eliminated with half-life of 2.1–3.8 hours. Exposure is dose related with no drug accumulation in the plasma. Common treatment-related adverse events included hematologic toxicity, hyperglycemia, hypocalcemia, increased liver enzymes, and diarrhea. The recommended phase II dose was 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle.

In addition, several inhibitors that target the signaling pathway for tissue homing, adhesion, and survival within the microenvironment are in clinical trials.[76] Examples include monoclonal antibodies (e.g., BMS-936564/MDX-1338, Bristol-Myers Squibb, New York, New York) and other antagonists (e.g., plerixafor, Mozobil, Sanofi-Aventis, Inc., Bridgewater, NJ) to the CXCR4 (chemokine receptor 4), a major receptor on nurse-like cells that mediate tissue homing and antagonist to the chemokine CXCL-12 (the ligand that binds to CXCR4). CXCR4 antagonist inhibits CXCL12- induced signaling, chemotaxis, and stromal cell–mediated drug resistance. Despite the concern that the CXCR4 antagonist may cause mobilization of normal hematopoietic stem cells and increase risk of hematologic toxicity when cytotoxic agents are given together with CXCR4 antagonist, the combination of plerixafor with cytotoxic chemotherapy resulted in no major hematologic toxicity.[77]

As discussed earlier, significant cytogenetic abnormalities (e.g., 17p deletion or *p53* mutation) within the CLL cells may influence prognosis and therapy sensitivity to cytotoxic chemotherapy by modulating the DNA damage response. The exploitation of the apoptosis machinery to bypass such resistance and trigger leukemic cell death may prove to be a winning concept. An antisense molecule that targets *BCL-2* (i.e., B-cell lymphoma-2, an oncogene responsible for the inhibition of apoptosis, thus leading to oncogenesis) has recently been developed under the name oblimersen. However, other prosurvival signals of the BCL-2 family members (e.g., MCL-1) may also contribute to the pathogenesis of CLL. Currently, investigational agents such as ABT-737, GX15-070, and AT-101 that target the apoptosis pathway are being evaluated for their role in CLL therapy.[78, 79]

Conclusion

Ibrutinib, obinutuzumab, and idelalisib represent an exciting addition to the growing armamentarium of therapeutic agents for CLL treatment. Ibrutinib is indicated in CLL patients who have received at least one prior therapy, whereas obinutuzumab is indicated for use in combination with chlorambucil for the treatment of patients with previously untreated CLL. Obinutuzumab may be a preferred first-line treatment option for CLL in patients older than 70 years with comorbidities, regardless of chromosomal abnormality. The optimal sequencing of these novel agents in CLL therapy remains to be defined. Together, new clinical trials will probably contribute to the redefinition of CLL treatment in either frontline or relapsed treatment setting or even both in the near future. Idelalisib acts as a downstream inhibitor in the BCR signaling pathway that is important for CLL cell survival and has demonstrated promising clinical activity in clinical studies, both as single-agent and in combination therapy.

B-cell receptor and downstream signaling pathways promise to be an excellent source of preclinical and clinical targeted drug development and will likely continue to revolutionize the treatment paradigm of CLL. The challenges will be to individualize treatment goals, define optimal combination therapies, and integrate molecular markers for response prediction.

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