Chronic lymphocytic leukemia (CLL) is a mature B-cell lymphoid neoplasm characterized by the proliferation and accumulation of small CD5/CD19/CD23-positive lymphocytes in the blood, lymph nodes, spleen, liver and bone marrow [1]. It is the most prevalent leukemia in the western world with an estimated 15,720 new cases in 2014 and almost 4600 attributable deaths per year in the United States [2]. CLL is typically sensitive to a variety of cytotoxic drugs, but the disease is considered incurable. Cytotoxic agents, including chlorambucil, bendamustine and purine analogs, currently constitute the basis of the most frequently used therapeutic regimens [3]. In addition, anti-CD20 monoclonal antibodies (mAbs), rituximab and ofatumumab, and the anti-CD52 antibody alemtuzumab, alone or in combination with cytotoxic drugs, have been included for therapeutic options in this leukemia.

Recently, significant progress in the better characterization and understanding of the biology and prognosis of CLL has provided new opportunities for the development of innovative, more effective therapies for this disease. Several new mAbs directed against lymphoid cells have been developed and investigated in preclinical studies and clinical trials, some of which are highly active in chronic lymphoid malignancies and are potentially useful in the treatment of CLL [4]. In particular, obinutuzumab, a novel third-generation anti-CD20 monoclonal antibody, has been approved for use with chlorambucil in patients with previously untreated CLL [5]. In addition, B-cell antigen receptor (BCR) signal transduction inhibitors - ibrutinib (PCI-32765) and idelisibis (GS-1101, CAL-101) - have been investigated and recently approved for the treatment of CLL patients [6,7]. These drugs are available in oral preparations and are given as continuous treatment. BCR inhibitors induce rapid resolution of lymphadenopathy and a transient increase of lymphocytosis due to mobilization of CLL cells into the peripheral blood.

Obinutuzumab (Gazyva®, GA-101, RO507259, Roche and Genentech) is a novel third – generation fully humanized and optimized anti-CD20 IgG1 differing significantly from such other anti-CD20 mAbs as rituximab [8,9]. The antibody is based on proprietary GlycoMab(*) technology, which incorporates glycoengineered antibodies that specifically increase antibody-dependent cellular cytotoxicity (ADCC) and thereby increase immune-mediated target cell death. In a registrative, multicenter 3-arm randomized study (CLL11/BO21004) GA-101 plus chlorambucil (G-CLB) was compared with rituximab plus chlorambucil (R-CLB) or chlorambucil alone in previously untreated CLL patients with increased comorbidity [10]. In this study patients with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 ml/min were included. Overall response (OR) rate was 31.4% for chlorambucil alone, 77.3% for G-CLB and 65.7% for R-CLB. Complete response (CR) was 0%, 20.7% and 7%, respectively. The duration of progression free survival (PFS) was also longer for G-CLB (26.7 m) than for R-CLB (16.3 m) or chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for death, 0.41; 95% CI, 0.23 to 0.74; P=0.002). Grade 3-4 infusion-related reactions at first infusion were observed in 21% of the patients treated with G-CLB and 4% of the patients treated with R-CLB. Moreover, grade 3-5 adverse events during treatment were noted more frequently in the G-CLB arm (67%) than in the R-CLB (46%) or chlorambucil arm (41%), grade 3-5 neutropenia was observed in 34%, 25% and 15% of cases in each respective arm, and grade 3-5 infections developed in 6%, 8% and 11%. The U.S. Food and Drug Administration (FDA) and European Medicinal Agency (EMA) have approved obinutuzumab for use with chlorambucil in patients with previously untreated CLL [5].

Ibrutinib (PCI-32765; Imbruvica, Janssen – Cilag International NV / Pharmacyclics) is an orally bioavailable, first-in-class, covalent inhibitor of Bruton’s tyrosine kinase (BTK) a critical enzyme in the BCR signalling pathway, which is essential for B-cell proliferation, survival, migration, and tissue homing [11]. Recent reports indicate that ibrutinib is well-tolerated and active in CLL patients [12-15]. Treatment with ibrutinib is associated with a high frequency of durable remissions in patients with previously untreated and relapsed or refractory CLL, including patients with high-risk genetic lesions, including 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. In a phase Ib/II multicenter study, ibrutinib was evaluated in 85 patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) [13]. The patients received ibrutinib orally once daily; 51 received 420 mg, and 34 received 840 mg. The OR rate was 71% in both groups, and an additional 20% and 15% of patients in the respective groups displayed a PR with lymphocytosis. The drug was highly active in heavily pretreated patients, with advanced-stage disease and the 17p13.1 deletion. At 26 months, the estimated PFS rate was 75% and the rate of OS was 83%. Subsequently, ibrutinib was compared with ofatumumab in a randomized, multicenter, open-label, phase III study in previously-treated patients with relapsed or refractory CLL or SLL [14]. The trial was prematurely stopped after interim analysis because of an improvement in PFS and OS in the ibrutinib arm. The OR rate was 42.6% in the ibrutinib group and 4.1% in the ofatumumab group (P<0.001). At 12 months, the OS rate was 90% in the ibrutinib arm and 81% in the ofatumumab arm. An additional 20% of ibrutinib-treated patients had a partial response with lymphocytosis. The improvements were noted regardless of whether patients had a chromosome 17p13.1 deletion or resistance to purine analogues. In February 2012, the FDA expanded the approved use of ibrutinib (Imbruvica) to CLL patients who had received at least one previous course of therapy. In July 2014, the FDA approved a licence extension for use of ibrutinib in patients with CLL and a 17p deletion. Simultaneously, EMA approved ibrutinib to treat relapsed or refractory CLL.

Idelisib (Zydelig, Gilead Sciences Inc/Calistoga Pharmaceuticals),
is a first-in-class, selective oral inhibitor of phosphatidylinositol 3-kinase P110δ (PI3Kδ) which reduces proliferation, enhances apoptosis, and inhibits homing and retention of malignant B cells in lymphoid tissues [16,17]. In a phase I trial, idelalisib was evaluated in 54 heavily pretreated patients with relapsed/refractory CLL [18]. The patients possessed adverse characteristics including bulky lymphadenopathy, unmutated IGHV, and del17p and/or TP53 mutations. The OR rate was 72%, including 39% of PR and 33% of PR with treatment-induced lymphocytosis. Nodal responses were observed in 81% of patients. The most frequently noted grade ≥3 adverse events were pneumonia (20%), neutropenic fever (11%), and diarrhea (6%). The median PFS for all patients was 15.8 months. Idelalisib used in combination with rituximab +/- bendamustine also demonstrates impressive efficacy and good tolerability [19]. In a multicenter, randomized, placebo-controlled, phase III study comparing rituximab with either idelalisib or placebo, the OR rate was 81% vs 13% and OS values at 12 months were 92% vs. 80%, respectively [20]. Serious AEs were similar in both arms and occurred in 40% of the patients receiving idelalisib + rituximab and in 35% of those receiving rituximab alone. In July 2014, the FDA approved Zydelig® (idelalisib) for the treatment of CLL. Simultaneously, the European Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the EMA, recommended the granting of marketing authorisation for the use of Zydelig in combination therapy for the treatment of patients with CLL. Ibrutinib is indicated in combination with rituximab for patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy.

In conclusion, recent clinical studies have demonstrated that obinutuzumab, ibrutinib and idelalisib have significant clinical activity and an acceptable safety profile in patients with previously untreated and relapsed/refractory CLL. These findings constitute the basis of their approval for the treatment of this disease.

References