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 have 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 idelisib (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, RO5072759, Roche and Genentech) is a novel third-generation fully humanized and optimized anti-CD20 IgG1 differing significantly from 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 chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m). Treatment with G-CLB prolonged overall survival (OS) as compared with chlorambucil alone (hazard ratio for chlorambucil alone (11.1 m).
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 CL. 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 for the treatment of patients with CL. Ibrutinib is indicated in combination with rituximab for patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy.

References