Chronic lymphocytic leukemia therapy: new targeted therapies on the way

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Abstract

Introduction—The critical role of the tissue microenvironment and B cell receptor (BCR) signaling in chronic lymphocytic leukemia (CLL) pathogenesis, and the clinical success of targeted agents that disrupt BCR signaling are currently changing the CLL landscape. Three new drugs were recently approved for CLL therapy, and other agents are in late development.

Areas covered—In this review, we summarize data on promising new targeted drugs for CLL. The heterogeneous mechanisms of actions of these molecules are described, such as the inhibition of BCR signaling, direct targeting of CD20 molecules on the CLL cell surface, and BCL-2 inhibition. We present preclinical and clinical data from phase I to III studies in order to describe efficacy and side effect profile of these new drugs. Data are derived from peer-reviewed articles indexed in PubMed and from abstracts presented at major international meetings.

Expert opinion—Ibrutinib and idelalisib are challenging the role of chemo-immunotherapy in CLL therapy in the frontline and relapsed disease settings. High-risk CLL patients particularly benefit from these new agents. Venetoclax and obinutuzumab are other effective agents added to our therapeutic armamentarium. Studies to better define the optimal use of these drugs, alone, or rather in combination or sequenced are underway.

Keywords
chronic lymphocytic leukemia; anti-CD20 mAb; BCL-2 antagonist; BTK inhibitor; ibrutinib; obinutuzumab; PI3Kδ inhibitor; venetoclax

1 Introduction

The therapeutic landscape in chronic lymphocytic leukemia (CLL) has considerably changed over the past few years. Prior to that, patients with CLL were treated with chemotherapy (alkylating agents, i.e. cyclophosphamide, chlorambucil, and purine analogues, i.e. fludarabine) without any major impact on the overall disease outcome. In contrast, the addition of the anti-CD20 monoclonal antibody (mAb) rituximab to the combination of fludarabine and cyclophosphamide (FCR) as chemo-immunotherapy[1] induced higher
overall response rates (ORR), longer progression-free survival (PFS) and longer overall survival (OS) when compared to fludarabine and cyclophosphamide chemotherapy alone[2]. The median PFS in CLL8 trial for patients receiving FCR was 4.8 years, although a longer median PFS of 6–7 years was reported in a phase II trial conducted at The University of Texas MD Anderson Cancer Center[2, 3], and FCR regimen is currently considered standard frontline treatment for young fit patients with CLL. Nevertheless, the majority of patients with CLL, due to age, comorbidity, or presence of high-risk disease features [unmutated IGHV, del(17p)], are not well suited for this treatment modality.

Significant progress in the understanding of CLL biology recently led to the identification of a series of new molecules that can more specifically target CLL cells. These new drugs are now approved or in a late stages of clinical development, and some of them are already considered of first choice for selected patients as per international guidelines[4]. The mechanism of action and target effects of these drugs are depicted in Table 1, whereas key clinical data are summarized in Table 2.

2 Bruton tyrosine kinase (BTK) inhibitors

The B cell receptor (BCR) is a transmembrane receptor expressed on the cell membrane of B cells. The binding of a specific antigen to the BCR triggers the activation of a cascade of intracellular signaling molecules, which are essential for normal B-cell development, survival, and proliferation, but are also involved in CLL pathogenesis, where they function in a similar fashion, promoting CLL cell survival and expansion[5, 6]. Antigen binding to the BCR leads to the recruitment of Lyn and Syk tyrosine kinases, which subsequently activate BTK[7]. BTK is named after Dr. Ogden Bruton, a pediatrician who described in 1952 the first case of Bruton’s agammaglobulinemia (X-linked agammaglobulinemia), a rare congenital immunodeficiency caused by missense mutations in the BTK gene, resulting in agammaglobulinemia and lack of mature B cells[8]. BCR signaling in CLL patients is characteristically activated in secondary lymphatic tissues[9], where CLL cells can encounter auto-antigens and microbial antigens[10] and where the CLL cells proliferate in a BCR signaling-dependent fashion in areas called “proliferation centers” or “pseudo-follicles”. BCR crosslinking with BCR-intrinsic motifs, termed autonomous BCR signaling, has been proposed as an additional alternative mechanism for BCR pathway activation[11]. BTK in turn activates downstream targets including phospholipase Cγ2 (PLCγ2) and NFκB[12].

2.1 Ibrutinib

2.1.1 Ibrutinib mechanism of action—Ibrutinib (PCI-32765) is an orally available small molecule inhibitor that covalently bonds with BTK at the C481 residue. This binding leads to an irreversible inhibition that hinders the kinase activity and results in a blockade of downstream signaling in vitro and in vivo. As a result, ibrutinib inhibits BCR signaling and consequently BCR signaling-dependent proliferation and survival of CLL cells[13–15]. In addition to its effects on BCR signaling, ibrutinib also inhibits the signaling of other cell surface receptors, including chemokine receptors and adhesion molecules which regulate the migration of CLL cells in response to chemotactic factors (chemotaxis) and their adhesion.
These effects on CLL tissue-homing and –retention mechanisms contribute to the characteristic clinical activity of ibrutinib and related kinase inhibitors, which cause redistribution of tissue-resident CLL cells into the peripheral blood, resulting in a transient increase in peripheral blood leukemia cell counts during the first months of treatment.

Ibrutinib also inhibits the BCR signaling-dependent secretion of CCL3/CCL4 by CLL cells[15], which normally function as CLL cell-derived chemo-attractants to recruit T cells and monocytes to sites of activated and proliferating CLL cells within the tissues. Finally, ibrutinib significantly delays disease progression in preclinical mouse models of CLL[15–17].

2.1.2 Ibrutinib in clinical trials—The activity of ibrutinib was first shown in a phase I trial that enrolled 16 relapsed/refractory patients with CLL (over a total of 56 patients with various B-cell malignancies)[18]. Different dose regimens were tested and the dose escalation could proceed up to 12.5 mg/kg per day without reaching any dose limiting toxicities. However, lower doses (2.5 mg/kg per day) were sufficient to obtain full occupancy of the BTK enzyme. The reported ORR was 54% for the entire patient population, and 69% for the CLL cohort. Based on the promising efficacy and safety data from this trial, a multi-center phase Ib/II clinical trial was conducted in 85 heavily pretreated patients with relapsed/refractory CLL or small lymphocytic lymphoma (SLL)[19]. Two different dose cohorts were studied (continuous daily dose of 420 mg or 840 mg), and after a median follow-up of 20.9 months the ORR was 71% (CR 3%; partial response, PR 68%). The response was superimposable in the two dose cohorts. Notably, the ORR increased to 90% at a longer follow-up of 3 years[20]. Based on the characteristic response pattern a new response category was defined for patients meeting the requirements for PR according to 2008 IWCLL criteria[21], but having persistent lymphocytosis (PR with persistent lymphocytosis, PRL; 20% in the 420 mg cohort and 15% in the 840 mg cohort). Importantly, responses were observed independently from the presence of high-risk prognostic factors. For example, patients with del(17p) achieved an ORR of 68%, with a 26-month estimated rate of PFS of 57%, comparing extremely favorable with historical data for patients with the same negative prognostic profile, even when treated frontline with conventional chemoimmunotherapy[2, 22]. Most reported adverse events (AE) were grade 1 or 2. Grade 1–2 AE occurring in >20% of patients were: diarrhea, upper-respiratory tract infection, fatigue, cough, arthralgia, rash, pyrexia, and edema, and muscle spasm. The most common grade ≥3 AE were pneumonia (10 patients, 12%) and dehydration (5 patients, 6%). Four cases of grade 3–4 bleeding events were reported, and therefore patients taking warfarin were excluded from the subsequent trials. The bleeding occurrence in patients treated with ibrutinib might be an on-target effect, given the role of BTK in platelet aggregation[23], and the activity of ibrutinib in inhibiting collagen and von Willebrand factor-dependent platelet adhesion and aggregation[24, 25].

Ibrutinib was also tested as frontline therapy in older patients (≥65 years)[26], resulting in an ORR of 71%, with 4 patients (13%) achieving a CR. The estimated 2-year PFS was 96.3%, and 2 year OS was 96.6%. The durability of responses to ibrutinib in treatment-naive and relapsed/refractory patients with CLL or SLL was confirmed in a recent study update of the two original trial cohorts after a median follow-up of 3 years[20]. Median PFS was not
reached for both groups of patients. The estimated PFS rate at 30 months was 96% for untreated patients, and 69% for relapsed/refractory patients. Progression events occurred mainly in relapsed patients with del(17p). The mechanisms leading to the loss of response to ibrutinib are not fully understood, but ibrutinib resistance has been associated in several cases with point mutations in BTK at the ibrutinib binding site and in the downstream signaling molecule PLCγ2[27], resulting in impaired ibrutinib binding or enhanced downstream signaling, respectively.

Ibrutinib was compared to ofatumumab in a phase III randomized trial (RESONATE) in 391 patients with relapsed/refractory CLL who were considered inappropriate for treatment with purine analogues[28]. Although in part expected based on the data on ofatumumab efficacy in CLL (58% ORR and median PFS of 5.7 months in patients refractory to fludarabine and alemtuzumab[29]), it was an important reassurance that patients treated with ibrutinib had significantly higher response rates (63% vs 4%) and longer median PFS (not reached vs 8.4 months after a median follow-up of 9.4 months). Importantly, the study also demonstrated a survival advantage for ibrutinib-treated patients (one-year OS 90% vs 81%; HR for death 0.43, 95% CI 0.24–0.79; p=0.005). The significant difference in efficacy between the two drugs was also observed in the cohort of patients carrying del(17p), and in patients resistant to purine analogues. AE reported in ≥20% of patients in the ibrutinib arm were diarrhea, fatigue, pyrexia, and nausea. The incidence of AE was higher in the ibrutinib arm generally due to longer drug exposure, and specific ibrutinib-related signals were higher incidence of atrial fibrillation (3% vs 0%), milder (but not severe) bleeding events, and cataracts (3% vs 1%).

The RESONATE-2 trial randomly assigned 269 elderly untreated patients with CLL or SLL to receive either ibrutinib or chlorambucil[30]. Patients with a known del(17p) were excluded from this study. Treatment with ibrutinib induced a significantly higher rate of response (ORR including PRL 88% vs 35%), a longer median PFS (not reached vs 18.9 months), and a longer OS (98% vs 85% at 2 years). All grade AE reported in ≥20% of patients in the ibrutinib arm were diarrhea (42% vs 17%), fatigue (30% vs 38%), cough (22% vs 15%), and nausea (22% vs 19%). Main grade 3–4 AE in the ibrutinib arm were neutropenia (10% vs 18%), anemia (6% vs 8%), hypertension (4% vs 0%), and diarrhea (4% vs 0%). In 4% of patients treated with ibrutinib a major hemorrhage was observed (no fatal events), and 6% developed atrial fibrillation (75% grade 2).

In a recently published single-arm phase II study, ibrutinib was specifically evaluated in 35 previously untreated and 16 relapsed/refractory CLL patients with del(17p) or TP53 aberrations[31]. Responses (including PRL) were observed in 97% of untreated patients and in 80% of relapsed/refractory patients after a median follow-up of 2 years.

Based on all these results, ibrutinib was approved in the US and in Europe for the treatment of patients with relapsed CLL, and for treatment-naive patients carrying a del(17p) or a TP53 mutation.

Combination studies were also designed to potentially increase the response rate and prolong the response duration, especially in patients considered to be at high risk of relapse.
or progression. In fact, it has been shown that patients who progress after responding to ibrutinib therapy, which generally are heavily pre-treated high-risk patients, often with del(17p), have a very poor prognosis\[32, 33\].

Ibrutinib in association with rituximab was studied in a phase II study in 40 patients with high-risk CLL based on presence of unfavorable cytogenetic abnormalities [del(17p), TP53 mutation, or del(11q)] or a short PFS <36 months after previous first-line chemo-immunotherapy. The ORR was 95% with the ibrutinib-rituximab combination, with 8% of patients achieving a CR. The PFS at 18 months was 78% in all patients, and 72% in those with del(17p) or TP53 mutation. The therapy was overall well tolerated and the most common adverse events were respiratory infections[34].

The combination of ibrutinib with chemo-immunotherapy is also under investigation, and the results of a small-scale phase Ib study exploring safety and efficacy of ibrutinib in association with FCR or bendamustine and rituximab (BR) in relapsed/refractory patients have been recently published[35]. BR-ibrutinib induced an ORR of 93%, including 17% CR (which increased to 40% with longer follow-up). PFS at 36 months was 70%. All 3 patients treated with ibrutinib-FCR achieved CR. As expected, the spectrum of AE recapitulates that of ibrutinib and chemo-immunotherapy, when used individually.

Ibrutinib combined with BR was recently compared with BR + placebo in an international, double-blind, placebo-controlled, phase III study (HELIOS) for relapsed/refractory patients with CLL or SLL[36]. A total of 578 patients were enrolled and patients with del(17p) or with CLL considered refractory to bendamustine were excluded. The ORR was significantly higher in the ibrutinib cohort compared to the placebo cohort (83% vs 68%). CR/CRi were achieved in 10% of patients in the ibrutinib group and in 3% of patients in the placebo group, and in the intention-to-treat population minimal residual disease (MRD) negative patients accounted for 13% and 5% in the ibrutinib and placebo group, respectively. The addition of ibrutinib significantly prolonged the median PFS (not reached vs 13.3 months, at a median follow-up of 17 months). The most frequent all-grade AE were neutropenia (59% and 55% in the ibrutinib and placebo group, respectively), nausea (38% and 36% in the ibrutinib and placebo group, respectively), and diarrhea (35% and 21% in the ibrutinib and placebo group, respectively). The overall proportion of patients with AE of grade 3–4 was similar between the two treatment groups (77% in the ibrutinib group and 74% in the placebo group). The most common grade 3–4 AE in both groups were neutropenia (54% and 51% in the ibrutinib and placebo group, respectively), and thrombocytopenia (15% in both groups). Overall, the safety profile was similar to that previously reported with ibrutinib and BR individually.

2.2 Acalabrutinib

Acalabrutinib (ACP-196) is a second generation BTK inhibitor which shares with ibrutinib the same mechanism of action, but has been designed to be a more potent and selective inhibitor of BTK, therefore potentially avoiding off-target side effects. The results of a phase I/II study exploring the safety and efficacy of oral acalabrutinib have been recently published[37]. A total of 61 patients with relapsed CLL were treated showing a favorable toxicity profile, the most common AE were headache (43% overall, 0% grade 3–4), weight
gain (26% overall, 2% grade 3–4), pyrexia (23% overall, 3% grade 3–4), and upper respiratory tract infections (23% overall, 0% grade 3–4). The reported ORR was 95% (85% PR and 10% PRL) for the entire patient population, and 100% (89% PR and 11% PRL) for the del(17p) cohort. The drug is further developed in ongoing phase III trials, one comparing acalabrutinib versus ibrutinib in relapsed/refractory CLL patients with high risk disease features (NCT02477696), and another comparing obinutuzumab + chlorambucil versus obinutuzumab + acalabrutinib versus acalabrutinib monotherapy in treatment-naïve CLL patients (NCT02475681).

3 Phosphatidylinositol-3-kinase inhibitors

Phosphatidylinositol-3-kinase (PI3K) is another cytoplasmic tyrosine kinase involved in the signaling pathway downstream of the BCR (and other surface receptors). After the phosphorylation of cytoplasmic domains of CD19 by Lyn, PI3K is recruited and activated, generating a lipid second messenger molecule, phosphatidylinositol-(3,4,5)-triphosphate (PIP3). Subsequently, other downstream signaling proteins are recruited and activated including phosphatidylinositol-dependent kinase 1 (PDK1)[7]. PIP3 is essential for BTK recruitment and PLCγ2 activation, therefore linking PI3K function with Ca²⁺ signaling[38]. Downstream, the activation of signaling pathways dependent on Akt and mammalian target of rapamycin (mTOR) influences cell metabolism, proliferation, DNA repair, survival, cytoskeleton changes and migration[7, 39]. PI3Ks are classified into three classes (I, II, III), and class I is further composed by four different isoforms (α, β, γ, δ). Isoforms α and β are widely expressed in many tissues, whereas isoforms γ and δ are restricted to hematopoietic cells. PI3Kδ is the form predominantly expressed by hematopoietic cells and plays a critical role in B cell homeostasis and function[39]. The knockout of the PI3Kδ gene in mouse models leads to B-cell deficiency, confirming the critical role of this signaling molecule in B-cell development and function[40, 41]. Moreover, PI3Kδ signaling pathway has been shown to be dysregulated in many solid cancers and is constitutively active in CLL[42, 43].

3.1 Idelalisib

3.1.1 Idelalisib mechanism of action—Idelalisib (GS-1101, CAL-101) is an orally available reversible inhibitor of the δ isoform of PI3K, causing a decrease in phosphorylation of several downstream targets including Akt. The effect of the interruption of the BCR signaling pathway is a disruption of the interactions between CLL cells and tumor microenvironment, as well as direct induction of leukemia cell apoptosis[44, 45].

3.1.2 Idelalisib in clinical trials—Idelalisib was initially evaluated in a phase I trial in 54 patients with relapsed/refractory CLL with adverse clinical and biological features[46]. Patients were treated for 48 weeks with daily idelalisib given continuously at different dose regimens (50 mg bid, 100 mg bid, 300 mg qd, 150 mg bid, 200 mg bid, 350 mg bid). The observed ORR was 72%, with 39% of patients achieving a PR and 33% achieving a PRL. The identified optimal dose was 150 mg twice daily, with a median PFS for patients receiving this dose or higher of 32 months, compared with 7 months for those receiving lower doses. The median OS was not reached, with 75% of patients surviving at 36 months. Thirteen patients had a del(17p) and the ORR in this group was 58%, with a median PFS of
3 months. Frequently reported AE included: fatigue (32%), diarrhea (48%), pyrexia (32%), cough (29%), back-pain (22%) and transaminase elevation (28%). Sixty-seven% of patients experienced a serious AE (mainly related to infectious complications) and 13% discontinued therapy due to an AE. Unexpected non-infectious serious AE included colitis (5.6%) and interstitial pneumonitis (1.9%).

The results of a phase III randomized trial comparing the activity of idelalisib (150 mg bid) in combination with rituximab vs placebo + rituximab were recently published[47]. The trial enrolled 220 patients with relapsed CLL who had progressed within 24 months of their last treatment, had previously received at least one treatment regimen including an anti-CD20 mAb or two or more cytotoxic regimens, and were deemed not eligible to receive cytotoxic chemotherapy (due to significant myelosuppression, a creatinine clearance of <60 ml/min or a cumulative illness rating scale [CIRS] >6). Patients in both treatment arms received 8 doses of rituximab, and patients on placebo were eligible to crossover and receive idelalisib if disease progression occurred. For 176 evaluable patients (88 in each arm) the ORR was significantly higher in patients receiving idelalisib (81% vs 13%, p<0.001). All responders had a PR. The response rate of the combination of idelalisib and rituximab was not affected by del(17p) or TP53 and IGHV mutational status. Patients in the idelalisib arm also had a prolonged PFS (93% vs 46% at 24 weeks; HR 0.15, 95% CI 0.08–0.28), and improved OS (92% vs 80% at 1 year; HR 0.28, 95% CI 0.09–0.86). Similar AE rates were reported in the two treatment arms. In the idelalisib arm, the five most common reported AE were pyrexia, fatigue, nausea, chills, and diarrhea. A grade 3 or greater elevation of hepatic transaminases occurred in 6% of patients, although it was not the reason for treatment discontinuation. Serious diarrhea and pneumonitis were more frequent in the idelalisib arm, but overall the treatment discontinuation rates were comparable between the two groups (8% vs 10% in the idelalisib and placebo groups, respectively). Gastrointestinal and skin disorders were the most common reasons for discontinuation in the idelalisib group. Due to the exceedingly favorable results observed in the idelalisib + rituximab arm, the trial was stopped early and idelalisib was approved, in combination with rituximab, in the US for the treatment of relapsed/refractory CLL patients, and in Europe for patients with relapsed/refractory disease or treatment-naïve with del(17p) or TP53 mutation and not candidate for chemo-immunotherapy.

The results obtained by idelalisib in combination with rituximab in treatment-naïve older (median age 71) patients have also been reported[48]. The ORR was 97% (including 19% CR), and PFS at 36 months was 83%. The side effect profile of this treatment combination is very characteristic, with a reported rate of grade 3–4 diarrhea/colitis of 42%, grade 3–4 AST/ALT elevation of 23%, grade 3–4 pneumonia of 19%, and grade 3–4 rash of 13%.

Recently, higher rates of AE were reported in a phase II study of idelalisib in combination with ofatumumab in previously untreated patients with CLL (n=21)[49]. Grade 3–4 transaminitis was observed in 57% of patients, grade 3–4 enterocolitis in 14%, and grade 3–4 pneumonitis in 10%. Preclinical data and responsiveness to corticosteroids suggest an autoimmune etiology, and the association with younger age and higher absolute lymphocyte counts at baseline may recommend the need to formulate better selection criteria for patients treated with this agent in the frontline setting.

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Preliminary results of the combination of idelalisib with BR compared with BR + placebo have been recently presented[50]. This phase III, randomized, placebo-controlled study enrolled 416 patients with relapsed/refractory CLL and showed a significantly improved median PFS in the experimental arm when compared to the placebo arm (23 vs 11 months). The median OS was not reached in either cohort, but the HR for survival was statistically significant (HR=0.55; p-value 0.008; 95% CI 0.36–0.86). Grade 3–4 diarrhea was reported in 7.2% of patients in the idelalisib arm (vs 1.9% in the placebo arm) and incidence of serious AE pneumonitis was 1.4% (vs 0%). Transaminase abnormalities were observed more frequently in the idelalisib arm (any grade ALT 59.9% vs 30.6%, any grade AST 52.2% vs 27.8%, grade 3–4 ALT 21.3% vs 2.9%, grade 3–4 AST 15.5% vs 3.3%).

3.2 Duvelisib

3.2.1 Duvelisib mechanism of action—Duvelisib (IPI-145) is an oral small-molecule that potently inhibits both PI3K\(\gamma\) and PI3K\(\delta\) isoforms. It was initially developed to suppress the activity of different components of adaptive and innate immunity in autoimmune and inflammatory diseases[51]. Due to its effect in suppressing B cell proliferation, it is now also under investigation for the treatment of lymphoproliferative diseases. Ideally, the inhibition of both PI3K isoforms could achieve a broader inhibitory activity and enhanced efficacy[51]. In vitro studies confirmed both the activity of duvelisib in inducing apoptosis in primary CLL cells, including samples with poor prognostic markers, and its safety towards normal B and T lymphocytes[52].

3.2.2 Duvelisib in clinical trials—Preliminary results of an ongoing phase I trial with duvelisib in patients with relapsed/refractory CLL have been presented[53]. Duvelisib at a dose of 25 mg twice daily provided an optimal biologic effect (maximum pAKT inhibition in CLL cells, reduction in serum cytokines and chemokines, reduction in CLL cell proliferation index). ORR was 55% (n=49), including 1 CR and 26 PR, and it was similar irrespective of dose, or the presence of del(17p) or TP53 mutation. 83% of patients (38/46) achieved >50% reduction in lymphadenopathy by CT scan. Treatment emergent AE were similar across the dose range. The most common AE grade ≥3 were neutropenia (31%), thrombocytopenia (11%), febrile neutropenia (15%), and pneumonia (11%) (median of 7.3 treatment cycles, range 1.0–30.8).

Different studies evaluating the activity of duvelisib in combination with chemo-immunotherapy are currently recruiting patients (e.g. NCT02158091, NCT01871675). Moreover, a phase III study to compare duvelisib monotherapy (starting dose: 25 mg twice daily) versus ofatumumab is ongoing (NCT02004522).

4 BH3 mimetic compounds

The BCL-2 family of proteins are important regulators of the intrinsic apoptosis pathway, which integrates stress and survival signals and governs cell survival and death[54, 55]. The BCL-2 oncogene was first identified in follicular lymphoma, where the encoded protein is overexpressed as a result of the t(14;18)[56], but BCL-2 overexpression is also a contributor in the pathogenesis other lymphoid malignancies. In CLL the high expression of BCL-2 has been linked to the deletion or downregulation of microRNAs miR15a and miR16-1[57].

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This understanding led to the development of BH3 mimetic compounds that mimic the action of the BH3-only proteins, which are the natural antagonists of anti-apoptotic members of the BCL-2 family (reviewed in[58]). The first tested molecule was navitoclax (ABT-263), an orally bioavailable small molecule with an inhibitory activity on both BCL-2 and BCL-XL. It was initially studied for the treatment of CLL[59], but drug development later was abandoned due to toxicity, primarily thrombocytopenia.

4.1 Venetoclax

4.1.1 Venetoclax mechanism of action—Venetoclax (ABT-199, GDC-0199) is an orally available small molecule that binds with high affinity to BCL-2 and with low affinity to other BCL-2 family proteins (i.e. BCL-XL and BCL-W)[60]. Pivotal data showed that venetoclax has promising in vitro tumor cell killing activity, induces the regression of hematological tumors in murine models, and has reduced toxicity on platelets both ex vivo and in vivo compared to navitoclax[60].

4.1.2 Venetoclax in clinical trials—As of March 2016, venetoclax has not yet been approved for clinical use, but it is currently being tested in late-stage clinical trials for CLL. Preliminary results published for the first three patients with refractory CLL treated in the first-in-human clinical trial showed that a single dose of ABT-199 induced rapid tumor lysis and confirmed that specific BCL-2 inhibition is a valid approach for CLL therapy[60].

Venetoclax was evaluated as single agent in a phase I study for the treatment of high risk relapsed/refractory CLL and SLL[61]. After a dose-escalation phase in which patients received venetoclax ranging from 150 to 1200 mg/day (n=56), an expansion cohort was treated at a dose of 400 mg/day (n=60), based on balance of overall response and safety data. A stepwise intra-patient increase in dose (ramp-up) to the final dose was implemented due to the early events of tumor lysis syndrome. After a median follow-up of 17 months, the ORR was 79%, with a 20% CR and a 5% of MRD negative CR. In the dose-escalation cohort the median PFS was 25 months, whereas this data cannot be reliably estimated in the expansion cohort due to the short follow-up in this group. The 15-months PFS was estimated to be 66% (95% CI, 51 to 77). Patients carrying a del(17p) had a median PFS of 16 months (95% CI, 11 to 25). Tumor lysis syndrome occurred in 18% of patients in the dose-escalation cohort (clinical tumor lysis syndrome in 3 patients, laboratory-only tumor lysis syndrome in 7 patients). Two patients with clinical tumor lysis syndrome had severe sequelae, including one death. In the expansion cohort, only one patient had laboratory evidence of tumor lysis syndrome. In the entire patient group, most common AE were diarrhea (52%), upper respiratory tract infection (48%), nausea (47%), neutropenia (45%), and fatigue (40%). Most common grade 3–4 AE were neutropenia (41%), anemia (12%), and thrombocytopenia (12%).

Venetoclax in combination with rituximab was studied in a phase Ib trial in relapsed/refractory CLL patients[62]. Rituximab was added after the completion of the ramp-up phase and preliminary pharmacokinetic data suggested a negligible effect of rituximab on venetoclax exposure[63]. Of 49 patients evaluable for response, the ORR was 86% (CR/CRi 41%, nPR 2%, PR 43%). MRD on bone marrow was quantified in 40 patients and MRD-
negativity was achieved in 75% of patients who achieved a CR/CRi. Overall 26 patients (53% of the total) achieved MRD-negativity. At a median follow-up of 17.5 months, the median PFS has not been reached. Twelve-month and 24-month PFS is 87% and 84%, respectively, and 12-month OS is 94%. The most common treatment-emergent AE were neutropenia (55%), diarrhea (53%), nausea (49%), upper respiratory tract infection (45%), fatigue and pyrexia (each 37%), cough (35%), and headache (33%). The most common overall grade 3–4 AE were neutropenia (53%), thrombocytopenia (16%), anemia (14%), febrile neutropenia (12%), and leukopenia (10%). One death due to tumor lysis syndrome was reported. More mature results have yet to be published, but based on these preliminary promising data different phase II and III trials have been started to evaluate the efficacy of venetoclax alone or in combination with chemo-immunotherapy (e.g. NCT01671904, NCT01685892, NCT02427451, NCT02005471, NCT02242942).

5 Novel anti-CD20 mAb

CD20 is a transmembrane protein broadly expressed on the surface of normal and malignant B lymphocytes, with an incompletely understood physiologic role. The targeting of the CD20 molecule with specific mAb has dramatically improved outcomes B-cell lymphoproliferative diseases, including CLL[64]. Rituximab and ofatumumab are categorized as type I antibodies, and their cytotoxic activity is mainly dependent on complement activation[65]. They are currently widely used in CLL in combination with purine analogues and alkylating agents, whereas their efficacy as single agents is modest.

5.1 Obinutuzumab

5.1.1 Obinutuzumab mechanism of action—As opposed to type I, type II antibodies characteristically stimulate antibody-dependent cell-mediated cytotoxicity (ADCC)[65]. Obinutuzumab (GA101) is a fully-humanized type II IgG1 mAb that binds to the same epitope as rituximab, but has a unique glycoengineered Fc region which was designed to have a stronger binding affinity with effector cells[66]. Preclinical in vitro data confirmed an increased direct cell death and effector cell-dependent cytotoxicity induced by obinutuzumab, when compared to rituximab[66, 67].

5.1.2 Obinutuzumab in clinical trials—Initial phase I studies showed the activity of obinutuzumab as single agent in patients with different B-cell lymphomas[68, 69]. In the phase I/II GAUGUIN trial, single agent obinutuzumab was administered to 33 heavily pretreated relapsed/refractory CLL patients[70]. ORR was 62% in the phase I cohort (n=13) and 15% in the phase II cohort (n=20), with no CRs. The difference in response between the two cohorts was attributed to an imbalance in tumor burden (based on the sum of the 6 largest lymph nodes). Median PFS in the phase II cohort was 10.7 months and median duration of response was 8.9 months. Infusion-related reactions occurred in almost all patients but the majority were grade 1–2. Neutropenia grade 3–4 was reported in 54% and 20% of patients in phase I and II, respectively. Obinutuzumab was studied as frontline treatment in CLL patients with significant comorbidities (Cumulative Illness Rating Scale, CIRS, score >6 and/or creatinine clearance <70 mL/min) in a recent phase III study from the German CLL Study Group (GCLLSG)[71]. The study compared 3 treatment arms:
chlorambucil alone vs chlorambucil + rituximab (R-chlorambucil) vs chlorambucil + obinutuzumab (G-chlorambucil). The ORR and CR were higher in patients treated with G-chlorambucil as compared to the other arms (ORR: G-chlorambucil 77.3%, R-chlorambucil 65.7%, chlorambucil 31.4%; CR: G-chlorambucil 22.3%, R-chlorambucil 7.3%, chlorambucil 0%). The negativity of MRD was also evaluated as parameter of response, and the rate resulted higher in the obinutuzumab group compared with the rituximab group (bone marrow: G-chlorambucil 19.5% vs R-chlorambucil 2.6%; blood: G-chlorambucil 37.7% vs R-chlorambucil 3.3%). The addition of obinutuzumab significantly prolonged PFS compared with the other two groups (median PFS: G-chlorambucil 26.7 months, R-chlorambucil 15.2 months, chlorambucil 11.1 months), and this difference was seen in all patient subgroups, except for del(17p). An OS advantage was seen for patients treated with G-chlorambucil compared to those treated with chlorambucil alone (HR for death 0.41, 95% CI 0.23–0.74, p=0.002), but no significant OS difference was demonstrated between the rituximab and obinutuzumab containing groups. The obinutuzumab arm was characterized by a higher incidence grade 3–4 infusion-related reactions (20% during the first infusion, 0% during subsequent infusions), grade 3–4 thrombocytopenia (10%) and grade 3–4 neutropenia (10%), with no increase in the risk of infection in the obinutuzumab group. Based on the results of this study, obinutuzumab is now approved in the US and Europe for the treatment of previously untreated co-morbid CLL patients in combination with chlorambucil.

Obinutuzumab was also studied in combination with different chemotherapy agents. The phase Ib GALTON trial evaluated obinutuzumab in association with fludarabine and cyclophosphamide (G-FC, n=21) or bendamustine (G-B, n=20) in previously untreated fit CLL patients[72]. The ORR for the G-FC group was 62% (10% CR; 14% CRi), whereas it was 90% (20% CR, 25% CRi) in the G-B arm. No relapses or deaths were observed after a median follow-up of 20.7 months in the G-FC cohort, and 23.5 months in the G-B cohort. The main grade 3–4 AE were: neutropenia (G-FC 29%, G-B 50%), febrile neutropenia (G-FC 19%, G-B 10%), thrombocytopenia (G-FC 19%, G-B 10%), infections (G-FC 19%, G-B 5%), infusion-related reactions (G-FC 29%, G-B 10%), all grade 3–4 infusion-related reactions were at first obinutuzumab infusion).

6 Conclusion

New treatment options are now available for patients with CLL, and other drugs are currently in a late stage of development. The BCR signaling pathway can be targeted by BTK inhibitors (i.e. ibrutinib, acalabrutinib), or by PI3K inhibitors (i.e. idelalisib, duvelisib). Another important therapeutic target is BCL-2, which is inhibited by venetoclax. Moreover, a novel glycoengineered type II anti-CD20 mAb (obinutuzumab) has recently been approved. The majority of these drugs are administered orally, and their mechanism of action is novel and entirely different when compared to standard chemo-immunotherapy. The clinical data with the novel agents are highly promising, but the impact of these drugs on the long term outcome of patients with CLL still needs to be better defined. Today, the new drugs already have had a major impact on outcome in CLL patients with high-risk disease who characteristically have poor outcome with chemo-immunotherapy; many of these patients now have durable responses on ibrutinib- or idelalisib-based regimen.
7 Expert opinion

Novel agents recently approved for the treatment of CLL (ibrutinib, idelalisib, obinutuzumab) offer new options that already impact patients’ outcome, especially in CLL patients with high-risk disease (del(17p) or TP53 mutations, unmutated IGHV). In addition to these approved drugs, several other new molecules, which currently are tested in advanced stage clinical trials, likely will become available in the near future. These developments are highly promising, because more choices and more effective therapy for high-risk patients - who characteristically have inferior responses to chemo-immunotherapy - will improve the outcome of patients suffering from this leukemia. Nonetheless, the new agents also increase the complexity of CLL treatment algorithm, and many questions still remain unanswered about the optimal use of these agents in CLL.

Among the most exciting innovations related to these agents have been new important lessons about disease biology derived from clinical and translational studies. By interfering with the BCR signaling pathway, ibrutinib and idelalisib (and the second generation molecules) interfere with critical survival and growth circuits within the CLL cell clone, but they also disrupt the leukemia-promoting interactions (“cross talk”) between CLL cells and their tissue microenvironment. While already recognized prior to the use of ibrutinib and idelalisib, the success of the BCR signaling inhibitors now corroborates with solid clinical evidence the importance of the tissue microenvironment, chemokines and their receptors, and the BCR as central regulators in CLL pathogenesis. Redistribution of CLL cells from tissue sites into the peripheral blood, causing rapid shrinkage of enlarged nodes, and at the same time a transient increase of leukemia cell counts in the peripheral blood, which then over time undergo death “by neglect”, as they are removed from their nurturing microenvironment, is a class effect of the kinase inhibitors that primarily target BCR signaling. This phenomenon is immediately reversible and dependent on continuous presence of the inhibitor, and demonstrates the relevance of CLL cell recirculation between blood and tissues as part of the disease process. Notably, it has been shown that prolonged lymphocytosis is not associated with adverse outcomes after ibrutinib therapy[73]. There are currently no reported cases of ibrutinib-induced leukostasis, and leukapheresis is still not indicated in patients with CLL, however it is prudent to closely monitor patients with a high number of circulating lymphocytes to promptly detect signs and symptoms of leukostasis. Regarding the response evaluation, the need of new guidelines has been suggested[74], considering that lymphocytosis in the absence of other signs of disease progression should not be regarded as an indication of treatment failure.

Achievement of deep remissions with MRD-negativity after chemo-immunotherapy correlates with improved PFS and OS in CLL[75] and has traditionally been the ultimate goal of therapy. Long term follow-up of the original 300 patients treated with FCR at MD Anderson Cancer Center[76] showed a PFS of 53.9% at 12.8 years for patients with mutated IGHV, with a plateau on the PFS curve, and confirmed that MRD-negativity is highly predictive of long-term PFS after FCR therapy, particularly in patients with mutated IGHV. In contrast, responses to ibrutinib and idelalisib occur at a slower pace than with chemo-immunotherapy, and many patients who experience partial response may achieve durable responses with long-term disease control, or eventually CRs after longer treatment with
these kinase inhibitors. It is currently unclear whether the depth of remission translates into longer disease-free survival when treating with ibrutinib, idelalisib, and the related compounds. Venetoclax, in contrast to ibrutinib and idelalisib, can induce MRD-negativity in a larger proportion of patients, but it is unclear at this time whether this potential advantage translates into longer PFS. Therefore, it is expected that the clinical use and the relevance of MRD assessment will be adapted over the next few years, and probably will be used in a more individualized fashion, taking into account the clinical setting and therapeutic regimen, and treatment goals, which differ substantially among patients subsets, i.e. in younger and fit versus older patients with comorbidities.

A more challenging feature of the BCR pathway inhibitors is the fact that patients currently are treated continuously until disease progression or intolerable side effects occur. Current data are not mature yet to determine long-term tolerability of these medications, given that most patients have been treated for less than 5 years. Therefore, we have no robust experience about the occurrence of late effects, secondary malignancies, or Richter’s transformation as compared to chemo-immunotherapy.

Another issue related to long-term and potentially indefinite use of some of these new agents is the high costs that can burden our patients and the healthcare systems. This factor may limit the access of patients to some of these agents, especially in countries with limited/restricted budgets for medical expenses. Indefinite kinase inhibitor therapy has become standard of care in patients with chronic myeloid leukemia, but it is foreseeable that the emergence of increasing numbers of new targeted cancer drugs will deplete the healthcare funds in the next few years, even in countries with less restrictive policies or well-funded healthcare systems. The hope therefore is that combination therapy approaches may eventually result in deep remissions that allow for drug discontinuation, and clinical trials with such an endpoint are currently under development. Furthermore, the competition of several new agents for a limited group of patients already has resulted in price negotiations and modifications to make these agents more affordable and available in some countries.

The broadening of the therapeutic armamentarium in CLL demands for the definition of specific criteria for choosing one drug over the other. In the absence of head-to-head comparisons derived from phase III studies, the side effect profile of the different drugs could guide the physician’s choice. For example, the bleeding risk is a factor usually taken into account in patients considered for ibrutinib treatment. The analysis of 327 patients from two trials of single agent ibrutinib showed that major bleeding events are generally uncommon and mostly occur in patients taking concomitantly one or more anticoagulants and/or antiplatelet agents[77]. Moreover, a recent report demonstrated that the risk of bleeding events is highest during the first weeks after initiation of treatment and decrease over time, and that patients who are at higher risk could be counseled to avoid antiplatelet agents[78]. Even if the requirement of antiplatelets or anticoagulant agents is not an absolute contraindication for ibrutinib treatment - which can be proposed to patients based on risk-benefit considerations - due to the fact that patients with CLL are usually elderly and with comorbidities, attention should be posed to ibrutinib-related bleeding events, and monitoring of these patients should be implemented. Another AE that is often related to age and preexistent comorbidities in patients taking ibrutinib is atrial fibrillation. Regarding this side
effect, the recommendation is to monitor patients, with particular attention to the patients with a history of cardiac disease, especially atrial fibrillation.

The observation of characteristic treatment-emergent AE in patients treated with idelalisib, such as diarrhea/colitis, transaminitis and pneumonitis has led to the development of specific guidelines[79]. Although a definitive patho-mechanism for these AE has not been defined, preclinical and clinical data support an immune-mediated etiology. Therefore, particular attention in monitoring of these patients during treatment is necessary. A relevant factor that may also complicate the administration of both ibrutinib and idelalisib is their interference with drugs that are strong or moderate CYP3A inhibitors or inducers. Dose adjustment might be considered on an individual basis, based on risk-benefit considerations.

Regarding venetoclax, the occurrence of tumor lysis syndrome events has led to the implementation of a ramp-up dose increase with a strict monitoring of clinical and laboratory parameters, and IV fluid infusion is strongly recommended for patients who are at higher risk. These procedures impact the advantages in patient management related to the oral administration of the drug, and need to be taken into account when evaluating costs and practicability of this agent.

The analysis of treatment-emergent AE in patients treated with obinutuzumab has underlined a higher than expected rate of infusion-related reactions. These events are generally manageable and restricted to the first infusions of the drug, however they should not be underestimated given the elderly and comorbid population.

Combination trials which include new drugs are currently in development. Undoubtedly, the main questions to answer concern efficacy and tolerability, but also the cost issue will be critical. The durability of remissions in patients who achieve MRD-negative CR on regimen that include the new agents and who will have treatment discontinuation (versus continued kinase inhibitor therapy in control groups) will be explored. Among the different drug combinations that have been reported, ibrutinib and idelalisib enhance the efficacy of chemo-immunotherapy without significant added toxicity, but any added benefit from the chemo-immunotherapy backbone in these combinations has not been convincingly demonstrated, when compared to single-agent kinase inhibitor data. A longer follow-up and more mature data are needed to clarify whether the addiction of conventional chemotherapy drugs to BCR inhibitors will result in improved therapeutic results, maybe favoring MRD eradication. Venetoclax has high single-agent activity and synergy with various anti-cancer drugs in preclinical models of different B-cell malignancies[60], and preclinical studies support its combination with ibrutinib in CLL[80]. Despite the excellent results obtained with FCR, long-term remissions were achieved with chemo-immunotherapy only in lower-risk CLL patients, for whom this remains an attractive therapy option. Moreover, it should be considered that the proportion of patients with CLL deemed adequately fit – considering age and comorbidities - to receive FCR treatment is relatively small. Moving forward, many CLL patients and the vast majority of high-risk CLL patients will transition to therapy with the newer agents, given their favorable safety and efficacy profile. Conversely, chemo-immunotherapy will mostly be offered to younger low-risk patients who favor a limited duration of therapy and the prospect of long-term disease-free survival.
Acknowledgments

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References


49. Lampson BL, Matos T, Kim HT, et al. Idelalisib Given Front-Line for the Treatment of Chronic Lymphocytic Leukemia Results in Frequent and Severe Immune-Mediated Toxicities. Blood. 2015; 126(23):497–497. 2015-12-03 00:00:00.


Several new targeted agents were recently approved and are challenging established CLL treatment regimens.

- The BTK inhibitor ibrutinib and PI3Kδ inhibitor idelalisib induce high overall response rates and durable remissions, which mostly are partial remissions.

- The BCL-2 inhibitor venetoclax induces more complete remissions, but response durability is not yet well established.

- At the approved dose, the anti-CD20 mAb obinutuzumab has higher efficacy than rituximab.

- Disease eradication may become possible with combination therapy approaches of novel agents and/or with chemo-immunotherapy in low-risk CLL.

- Longer follow-up is needed to fully characterize the spectrum of side effects of the novel agents.
### Table 1

**Novel targeted agents under study in CLL**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Phase of development</th>
<th>Route of administration</th>
<th>Mechanism of action</th>
<th>Target effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib (PCI-32765)</td>
<td>Approved (US and Europe)</td>
<td>Oral</td>
<td>Small molecule inhibitor of BTK</td>
<td>Inhibition of BCR signaling-dependent proliferation, survival, and microenvironment interactions.</td>
</tr>
<tr>
<td>Acalabrutinib (ACP-196)</td>
<td>Phase III trials ongoing</td>
<td>Oral</td>
<td>Small molecule inhibitor of BTK (second generation)</td>
<td>More potent and selective inhibition of BTK as compared to ibrutinib.</td>
</tr>
<tr>
<td>Idelalisib (GS-1101, CAL-101)</td>
<td>Approved (US and Europe)</td>
<td>Oral</td>
<td>Small molecule reversible inhibitor of PI3K δ</td>
<td>Inhibition of BCR signaling-dependent proliferation, survival, and microenvironment interactions.</td>
</tr>
<tr>
<td>Duvelisib (IPI-145)</td>
<td>Phase III trials ongoing</td>
<td>Oral</td>
<td>Small molecule inhibitor of PI3K γ and δ</td>
<td>Inhibition of BCR signaling in CLL cells and inhibition of PI3K-dependent signaling in different cellular components of adaptive and innate immunity.</td>
</tr>
<tr>
<td>Venetoclax (ABT-199, GDC-0199)</td>
<td>Phase III trials ongoing</td>
<td>Oral</td>
<td>Small molecule with BH3-mimetic activity</td>
<td>Blocking of the BCL-2 anti-apoptotic activity, leading to programmed cell death.</td>
</tr>
<tr>
<td>Obinutuzumab (GA101)</td>
<td>Approved (US and Europe)</td>
<td>Intravenous</td>
<td>Fully-humanized type II IgG1 anti-CD20 mAb, with a glycoengineered Fc region</td>
<td>Induction of direct cell death and effector cell-dependent cytotoxicity.</td>
</tr>
</tbody>
</table>
## Table 2

Summary of key clinical data for novel agents in CLL

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target population</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Response</th>
<th>Survival</th>
<th>Main reported toxicities</th>
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<tr>
<td><strong>Ibrutinib</strong></td>
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<tr>
<td>Byrd et al. N Eng J Med, 2013[19] Phase Ib/II</td>
<td>Relapsed/refractory (n=85)</td>
<td>Ibrutinib 420 or 840 mg/day</td>
<td>Median follow-up 20.9 months</td>
<td>ORR 71% CR 3% PR 68% PRL 18%</td>
<td>26-month PFS 75% 26-month OS 83%</td>
<td>G3–4 pneumonia 12%, G3–4 dehydration 6%, G3–4 bleeding 5%</td>
</tr>
<tr>
<td>O’Brien et al. Lancet Oncol, 2014[26] Phase Ib/II</td>
<td>Untreated, age ≥65 (n=31)</td>
<td>Ibrutinib 420 or 840 mg/day</td>
<td>Median follow-up 22.1 months</td>
<td>ORR 71% CR 13% PR 67% PRL 13%</td>
<td>24-month PFS 96.3% 24-month OS 96.6%</td>
<td>G3–4 diarrhea 13%</td>
</tr>
<tr>
<td>Byrd et al. N Eng J Med, 2014[28] Phase III RESONATE</td>
<td>Relapsed/refractory, not candidate for purine analogues (n=391)</td>
<td>RCT: Ibrutinib 420 mg/day (n=196) vs ofatumumab (12 doses) (n=195)</td>
<td>Median follow-up 9.4 months</td>
<td>ORR 63% (vs 4%) CR 0% PR 43% PRL 20%</td>
<td>Median PFS not reached (vs 8.4 months) 12-month OS 90% (vs 81%)</td>
<td>G3–4 neutropenia 16% (vs 14%), any grade atrial fibrillation 5% (vs &lt;1%), any grade bleeding 44% (vs 12%)</td>
</tr>
<tr>
<td>Burger et al. Lancet Oncol, 2014[30] Phase III RESONATE-2</td>
<td>Untreated, age ≥65, del(17p) excluded (n=269)</td>
<td>RCT: Ibrutinib 420 mg/day (n=136) vs chlorambucil (up to 12 courses) (n=133)</td>
<td>Median follow-up 18.4 months</td>
<td>ORR including PRL 86% (vs 35%) CR/Cri 4% (vs 2%) PR 77% (vs 34%)</td>
<td>Median PFS not reached (vs 18.9 months) 24-month OS 98% (vs 85%)</td>
<td>G3–4 neutropenia 10% (vs 18%), G3–4 anemia 6% (vs 8%), G3–4 hypertension 4% (vs 0%), G3–4 diarrhea 4% (vs 0%), major hemorrhage 4%, any grade atrial fibrillation 6%</td>
</tr>
<tr>
<td>Burger et al. Lancet Oncol, 2014[34] Phase II</td>
<td>Relapsed/refractory, high risk (n=40)</td>
<td>Ibrutinib 420 mg/day + rituximab (9 doses)</td>
<td>Median follow-up 16.8 months</td>
<td>ORR 95% CR 8% PR 87%</td>
<td>18-month PFS 78% 18-month PFS in del(17p) or TP53 mutated 72% 18-month OS 84% 18-month OS in del(17p) or TP53 mutated 78%</td>
<td>G3–4 neutropenia 10% (vs 18%), G3–4 hypertension 5% (vs 0%), G3–4 thrombocytopenia 15% (vs 15%), any grade diarrhea 35% (vs 21%)</td>
</tr>
<tr>
<td>Chanan-Khan et al. Lancet Oncol, 2015[36] Phase III HELIOS</td>
<td>Relapsed/refractory, bendamustine-resistant and del(17p) excluded (n=578)</td>
<td>RCT: Rituximab + bendamustine + ibrutinib (420 mg/day) (n=289) vs rituximab + bendamustine + placebo (n=289)</td>
<td>Median follow-up 17 months</td>
<td>ORR 83% (vs 68%) CR/Cri 10% (vs 3%) PR 72% (vs 65%) MRD negative 13% (vs 5%)</td>
<td>18-month PFS 79% (vs 24%) Median OS not reached in both groups</td>
<td>G3–4 neutropenia 54% (vs 51%), G3–4 hypertension 7%, G3–4 increased weight 2%, G3–4 pyrexia 3%</td>
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</table>

**Acalabrutinib**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target population</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Response</th>
<th>Survival</th>
<th>Main reported toxicities</th>
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<tr>
<td>Byrd et al. N Eng J Med, 2014[37] Phase I-I</td>
<td>Relapsed (n=61)</td>
<td>Phase I: acalabrutinib 100–400 mg/day Phase II: acalabrutinib 100 mg BID</td>
<td>Median follow-up 14.3 months</td>
<td>ORR 95% CR 0% PR 85% PRL 10% ORR in del(17p) 100%</td>
<td>18-month PFS 96.7%</td>
<td>G3–4 diarrhea 2%, G3–4 hypertension 7%, G3–4 increased weight 2%, G3–4 pyrexia 3%</td>
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<tr>
<td>Trial</td>
<td>Target population</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>Response</td>
<td>Survival</td>
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<td><strong>Idelalisib</strong></td>
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<td>Brown et al. Blood, 2014[46] Phase I</td>
<td>Relapsed/refractory, high risk (n=54)</td>
<td>Idelalisib 50 mg bid up to 350 mg bid</td>
<td>Median follow-up NA</td>
<td>ORR 72% CR 0% PR 39% PRL 33%</td>
<td>Median PFS 15.8 months</td>
<td>G3–4 diarrhea 5.6%, G3–4 pneumonia 20.4%, G3–4 neutropenia 42.6%, G3–4 thrombocytopenia 16.7%</td>
</tr>
<tr>
<td>Furman et al. N Engl J Med, 2014[47] Phase III</td>
<td>Relapsed/refractory, ineligible for cytotoxic therapy (n=220)</td>
<td>RCT: rituximab (8 doses) + idelalisib 150 mg bid (n=110) vs rituximab (8 doses) + placebo (n=110)</td>
<td>Median follow-up NA</td>
<td>ORR 81% (vs 13%) PR 81%</td>
<td>24-week PFS 93% (vs 46%) 12-month OS 92% (vs 80%)</td>
<td>Any grade pyrexia 32% (vs 17%), any grade diarrhea 23% (vs 4%), G3–4 diarrhea 4% (vs 0%), any grade AST/ALT increase 40% (vs 20%), G3–4 AST/ALT increase 5% (vs 1%)</td>
</tr>
<tr>
<td>O’Brien et al. Blood, 2015[48] Phase II</td>
<td>Untreated, age ≥65 (n=64)</td>
<td>idelalisib 150 mg bid rituximab (8 doses)</td>
<td>Median follow-up NA</td>
<td>ORR 97% CR 14% PR 83% ORR in del(17p) 100%</td>
<td>36-month PFS 82% 36-month OS 90%</td>
<td>Any grade diarrhea/colitis 64%, G3–4 diarrhea/colitis 42%, any grade AST/ALT increase 67%, G3–4 AST/ALT increase 23%, any grade pneumonia 28%, G3–4 pneumonia 19%, any grade rash 58%, G3–4 rash 13%</td>
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<tr>
<td><strong>Venetoclax</strong></td>
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<tr>
<td>Roberts et al. N Engl J Med, 2015[61] Phase I</td>
<td>Relapsed/refractory, high risk (n=116)</td>
<td>Dose-escalation: venetoclax 150–1200 mg/day Expansion: 400 mg/day (Weekly ramp-up to the final dose)</td>
<td>Median follow-up 17 months</td>
<td>ORR 79% CR 20% MRD negative CR 5% ORR in del(17p) 71% CR in del(17p) 16%</td>
<td>15-month PFS 66% 24-month OS 84%</td>
<td>All grade tumor lysis syndrome 18% in dose-escalation cohort (including 1 G5), 7% in expansion cohort, G3–4 neutropenia 45%, G3–4 anemia 12%, G3–4 thrombocytopenia 12%</td>
</tr>
<tr>
<td>Ma et al. ASH 2015[62] Phase Ib</td>
<td>Relapsed/refractory (n=57)</td>
<td>Venetoclax, weekly ramp-up to the final cohort dose (200–600 mg daily) + rituximab (6 doses)</td>
<td>Median follow-up 17.5 months</td>
<td>ORR 86% CR/CRi 41% PR/nPR 45% ORR in del(17p) 89%</td>
<td>12-month PFS 87% 24-month PFS 84% 12-month OS 94%</td>
<td>G3–4 neutropenia 53%, G3–4 thrombocytopenia 16%, G3–4 anemia 14%, G3–4 febrile neutropenia 12%. One G5 tumor lysis syndrome.</td>
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<tr>
<td><strong>Obinutuzumab</strong></td>
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<tr>
<td>Carrion et al. Blood, 2014[70] Phase I/I GAUGUIN</td>
<td>Relapsed/refractory (n=33)</td>
<td>Obinutuzumab 400–1200 mg for 9 doses in phase I and 1000 mg for 10 doses in phase II</td>
<td>Median follow-up phase I: 38.7 months Median follow-up phase II: 26.8 months</td>
<td>ORR phase I 62% ORR phase II 15% CR 0%</td>
<td>Median PFS in phase II 10.7 months</td>
<td>All grade infusion-related reactions 97% (majority grade 1–2). G3–4 neutropenia 54% and 20% in phase I and II, respectively</td>
</tr>
<tr>
<td>Goede et al. N Eng J Med, 2014[71] Phase III CLL11</td>
<td>Untreated, with comorbidities (n=781)</td>
<td>RCT: obinutuzumab (8 doses) + chlorambucil (O-chlorambucil, n=333) vs rituximab (6 doses) +</td>
<td>Median follow-up NA</td>
<td>ORR G-chlorambucil 77.3% ORR R-chlorambucil 65.7%</td>
<td>Median PFS G-chlorambucil 26.7 months, R-chlorambucil 15.2 months, chlorambucil 11.1 months</td>
<td>O-chlorambucil: grade 3–4 infusion-related reactions 20% during the first infusion, 0% during subsequent infusions, grade 3–4 thrombocytopenia 10%, grade 3–4 neutropenia 10%</td>
</tr>
<tr>
<td>Trial</td>
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<td>chlorambucil (R-</td>
<td>chlorambucil, n=330) vs chlorambucil (n=118)</td>
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<td>ORR chlorambucil 31.4% CR G-chlorambucil 22.3% CR R-chlorambucil 7.3% CR chlorambucil 0% MRD negativity bone marrow G- chlorambucil 19.5% (vs R-chlorambucil 2.6%) MRD negativity blood G-chlorambucil 37.7% (vs R-chlorambucil 3.3%)</td>
<td>Median OS not reached</td>
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