

UC Irvine

UC Irvine Previously Published Works

Title

Three Newly Approved Drugs for Chronic Lymphocytic Leukemia: Incorporating Ibrutinib, Idelalisib, and Obinutuzumab into Clinical Practice

Permalink

<https://escholarship.org/uc/item/1qb4d77b>

Journal

Clinical Lymphoma Myeloma & Leukemia, 15(7)

ISSN

2152-2650

Authors

Sanford, David S
Wierda, William G
Burger, Jan A
[et al.](#)

Publication Date

2015-07-01

DOI

10.1016/j.clml.2015.02.019

Peer reviewed



HHS Public Access

Author manuscript

Clin Lymphoma Myeloma Leuk. Author manuscript; available in PMC 2016 July 01.

Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2015 July ; 15(7): 385–391. doi:10.1016/j.clml.2015.02.019.

Three newly approved drugs for chronic lymphocytic leukemia (CLL): Incorporating ibrutinib, idelalisib and obinutuzumab into clinical practice

David Sanford, William G. Wierda, Jan A. Burger, Michael J. Keating, and Susan M. O'Brien

Department of Leukemia, University of Texas – MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030 Tel -713-745-0394

David Sanford: dsanford@mdanderson.org; William G. Wierda: wwierda@mdanderson.org; Jan A. Burger: jaburger@mdanderson.org; Michael J. Keating: mkeating@mdanderson.org

Abstract

Three agents have received FDA approval for treatment of chronic lymphocytic leukemia (CLL) within the last year. Ibrutinib and idelalisib block B-cell receptor signaling through inhibition of BTK and PI3K δ molecules respectively, interfering with several pathways required for leukemia cell survival. Idelalisib has shown efficacy in the relapsed setting and is currently approved for use in combination with rituximab. Ibrutinib has been studied in patients with relapsed CLL and as frontline therapy. In the relapsed setting, these agents produce durable remissions, and may be preferable to retreatment with chemoimmunotherapy for many patients. Ibrutinib is also effective treatment for patients with deletion 17p and is approved as frontline therapy in this patient group, although it does not appear to completely abrogate this adverse prognostic factor. These agents have a unique side effect profile and longer follow-up is required to further understand tolerability and rare adverse effects. Obinutuzumab is a type-2 monoclonal anti-CD20 antibody which results in direct and antibody-dependent cell-mediated cytotoxicity of leukemia cells. It is approved in combination with chlorambucil, and has shown efficacy in the frontline setting in patients unfit for more intensive chemoimmunotherapy. It produces increased response rates and minimal residual disease (MRD) negativity in comparison with chlorambucil/rituximab and is associated with an advantage in progression free survival but not yet overall survival. These agents underscore our advancement in the understanding of the biology of CLL and will improve outcomes for many patients with CLL.

Keywords

chronic lymphocytic leukemia; ibrutinib; idelalisib; obinutuzumab; novel agents

Corresponding Author: Susan M. O'Brien, Chao Family Comprehensive Cancer Center, UC Irvine Medical Center, 101 The City Drive South, Orange, CA 92868, Phone: 714-456-7890, obrien@uci.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures

David Sanford None

Michael J. Keating None

Introduction

Signaling through the B-cell receptor plays an important role in survival and proliferation in chronic lymphocytic leukemia (CLL) and occurs in a constitutive, antigen-independent manner.¹ Within the last year, inhibitors targeting B-cell signaling pathways, ibrutinib and idelalisib, as well as the novel anti-CD20 monoclonal antibody, obinutuzumab, have been approved for use in CLL by the FDA. These agents herald a new generation of targeted therapy in CLL, and we anticipate they will alter the treatment of CLL in the frontline and in the relapsed setting. The promise of these agents is offset by unanswered questions about the long-term efficacy and safety, as well as how to best incorporate them with other agents. This review addresses the mechanisms of action underlying these novel agents, summarizes the recent clinical trials supporting their use in CLL, and provides suggestions for their use in specific clinical settings.

Idelalisib

Mechanism of action

During normal B-cell signaling, binding of antigen to the B-cell receptor (BCR) recruits *Lck/Yes novel tyrosine kinase (Lyn)*, a Src tyrosine kinase, as well as *Spleen Tyrosine Kinase (Syk)* to the intracellular *Immunoreceptor Tyrosine Activation Motifs (ITAMs)* of CD79a and CD79b.² Phosphorylation of cytoplasmic domains of CD19 by Lyn leads to recruitment and activation of lipid kinase *phosphatidylinositol 3-kinase (PI3K)*, the target of idelalisib.² PI3K generates a lipid second messenger molecule *phosphatidylinositol (3,4,5) triphosphate (PIP3)*, which recruits several other signaling proteins to the inner surface of the lipid membrane and activates *phosphatidylinositol-dependent kinase 1 (PDK1)*.² This results in activation of Akt (aka protein kinase B) and *mammalian target of rapamycin (mTOR)* signaling pathways which broadly influence cell survival, cytoskeleton changes, mobility, metabolism and DNA repair.²

Eight isoforms of PI3K are present in mammals with the class I isoform PI3K δ being predominantly expressed in immune cells, including B-cells.³ Mouse-models with knockout of the p110 δ -PI3K gene lead to severe B-cell deficiency suggesting a critical role of this signaling molecule in B cell development and function.^{4,5} PI3K is normally inhibited by tumor suppressor *phosphatase with tensin homology deleted on chromosome 10 (PTEN)*, which is known to be mutated or deleted in several types of solid tumors.⁶ Down-regulation of PTEN has also been reported to correlate with disease progression in CLL and the presence of adverse risk factor such as TP53 deletion.⁷ Dysregulation of PI3K δ signaling occurs in many solid cancers and this pathway appears to be constitutively active in CLL.^{8,9} Idelalisib (CAL-101) reversibly inhibits the p110 δ -PI3K isoform leading to decreased phosphorylation of several down-stream targets including Akt, ultimately disrupting interactions between tumor cells and the bone marrow microenvironment and chemokine signaling, as well as directly inducing apoptosis.^{10,11} Disruption of the microenvironment supporting tumor growth results in a significant increase in peripheral blood lymphocyte count that usually occurs within 1–2 weeks of starting treatment and gradually declines

thereafter. This phenomenon is not unique to idelalisib, and is also seen with ibrutinib and other B-cell receptor inhibitors.

Summary of clinical trials

Idelalisib is currently approved for use by the FDA in combination with rituximab for patients with relapsed/refractory CLL.¹² In a phase 1 trial, 54 patients with relapsed/refractory CLL were treated for 48 weeks with continuous daily idelalisib (doses: 50 mg bid, 100 mg bid, 300 mg qd, 150 mg bid, 200 mg bid, 350 mg bid). Responses were seen in 39 patients (74%, 95% CI 58.4%–83.5%) with 21 (39%) achieving a partial response and 18 (33%) achieving a partial response with treatment-induced lymphocytosis (PRL). The optimal dose appeared to be 150 mg twice daily and the median progression free survival (PFS) for patients receiving this dose or higher was 32 months compared with 7 months for those receiving lower doses. The overall response rate (ORR) in 13 patients with deletion 17p was 58%, although the reported median PFS of 3 months in this group was relatively short. Frequently reported adverse events included: fatigue (32%), diarrhea (48%), pyrexia (32%), cough (29%), back-pain (22%) and transaminase elevation (28%). Seven patients (12.9%) discontinued therapy due to an adverse event and 36 patients experienced a serious adverse event with the majority being related to infectious complications. Other non-infectious serious adverse events included colitis (5.6%) and interstitial pneumonitis (1.9%).

A phase 3 randomized control trial reported on the use of combined therapy with idelalisib and rituximab in patients with relapsed disease.¹³ Patients in the trial had progressed within 24 months of their last treatment and had received at least one previous treatment with a CD20 antibody-based regimen or two or more cytotoxic regimens. This trial included patients that were deemed not eligible for further cytotoxic chemotherapy due to significant myelosuppression related to prior chemotherapy, a creatinine clearance of <60 ml/min or a cumulative illness rating scale (CIRS) value of greater than 6. Participants (n=220) received 8 infusions of rituximab and were randomly assigned to idelalisib 150 mg PO BID or placebo starting on day 0 of treatment. Patients on placebo were eligible to crossover and receive idelalisib if disease progression occurred, although results after crossover are not yet available. Response rates reported for 176 patients that underwent at least 1 post-baseline assessment were significantly higher in the group receiving idelalisib (81% vs. 13%, Odds ratio 29.9 (p<0.001)). All responders had a partial response (PR). Improved PFS (24 week PFS: 93% vs. 46%, HR 0.15 (95% CI 0.08–0.28)) and overall survival (OS) (1 year OS: 92% vs. 80%, HR 0.28, (95% CI 0.09–0.86, p=0.02) were also seen in the idelalisib group. The reported adverse events were similar between the idelalisib and placebo groups and the five most commonly reported were pyrexia, fatigue, nausea, chills, and diarrhea. Grade 3 or greater elevation of hepatic transaminases occurred more frequently in the idelalisib group (6%) although no patients discontinued the medication for this reason. Non-infectious serious adverse events such as diarrhea and pneumonitis were more frequent in the idelalisib group. Rates of discontinuation were comparable between the idelalisib and placebo groups (8% vs. 10%) with gastrointestinal and skin disorders being common reasons for discontinuation in the idelalisib group.

Ibrutinib

Mechanism of action

Recruitment of Syk and Lyn during B-cell receptor signaling also leads to phosphorylation and activation of Bruton's Tyrosine Kinase (BTK).² BTK is required for normal B cell function and development and derives its name from Bruton's agammaglobulinemia (X-linked agammaglobulinemia), a rare congenital condition characterized by agammaglobulinemia, absence of mature B-cells and missense mutations in the BTK gene.¹⁴ After activation, BTK in turns phosphorylates phospholipase C γ 2 (PLC γ 2), leading to activation of downstream signaling pathways mediated through MAP kinase activation and NF κ B.² Mutations in the BTK gene have not been identified in CLL in studies using whole genome sequencing^{15,16}, although BTK appears to be overexpressed in many cases.¹⁷ Ibrutinib irreversibly binds to BTK at the C481 residue, preventing kinase activity and blocking downstream signaling pathways.¹⁸ In CLL, this prevents proliferation of leukemia cells and may also directly induce apoptosis, although the latter requires high drug concentrations not occurring with usual treatment doses.¹⁹ Ibrutinib also disrupts supportive interactions with the bone-marrow microenvironment by altering expression of adhesion molecules and interfering with expression of chemokines required for B-cell homing.²⁰

Summary of clinical trials

Ibrutinib (PCI-32765) was initially shown to have activity in a phase I trial involving 56 relapsed/refractory patients with non-Hodgkin lymphoma and included 16 patients with CLL.²¹ This dose-finding study enrolled 5 cohorts treated on a 28 day on/7 day off schedule with doses escalating from 1.25 to 12.5 mg/kg/day and 2 cohorts treated on a continuous dosing schedule at 8.3 mg/kg/day or a fixed 560 mg daily dose. Escalation to the 12.5 mg/kg/d dose was possible without dose limiting toxicity and full occupancy of the BTK enzyme was determined to occur at a relatively low dose of 2.5 mg/kg/d. The authors reported an overall response rate (CR+PR) of 54% for the entire cohort, including 11 of 16 patients with CLL.

Ibrutinib has been approved for patients with relapsed CLL on the basis of results of a multi-center phase Ib/2 clinical trial clearly demonstrating efficacy in heavily pre-treated patients.²² This group of 85 patients received a median of 4 prior therapies with the majority receiving previous treatment with purine analogues, rituximab and alkylating agents. Patients were treated with a continuous daily dose of 420 mg or 840 mg. The overall response rate of 71% (PR=58, CR=2) after a median follow-up of 20.9 months was identical between dose cohorts. As well, 18% of patients had a partial response with lymphocytosis (PRL), which was defined as a partial response in all measures according to IWG 2008 criteria, except for a persistent lymphocytosis.²³ The PFS and OS at 26 months were 75% and 83% respectively. Responses did not appear to be related to traditional cytogenetic prognostic factors, and 19/28 (68%) patients with a 17p deletion had a response including one complete response. The rate of overall response (CR + PR +PRL) did not differ significantly according to the mutation status of the variable region of the heavy chain gene. The most commonly reported (frequency >20% of participants) adverse events were: diarrhea, upper-respiratory tract infection, fatigue, cough, arthralgia, rash, pyrexia, edema,

and muscle spasm. There were 4 episodes of grade 3–4 bleeding events and subsequent trials using ibrutinib have excluded patients taking anticoagulants. Ibrutinib inhibits platelet aggregation to collagen, although the clinical relevance of this is not clear and warrants further study.²⁴ Responses to ibrutinib appeared to be durable in most patients, although 11 patients experienced disease progression, of which 7 were Richter's transformation. The development of resistance to ibrutinib is not well understood but resistance mutations in both BTK and down-stream signaling molecule PLC γ 2 have been described in some patients that have progressed on treatment.²⁵

A phase 3 randomized trial (*RESONATE*) comparing ibrutinib to ofatumumab in 391 patients with relapsed/refractory CLL has demonstrated a survival advantage of ibrutinib over single agent ofatumumab.²⁶ Single agent ofatumumab has a favorable safety and tolerability profile although modest efficacy in CLL; a study of ofatumumab monotherapy in CLL patients refractory to fludarabine and alemtuzumab reported an overall response rate of 58% (all PR) and a median PFS of 5.7 months (95% CI 4.5 to 8.0 months).²⁷ Ofatumumab is typically used as a single agent in the treatment of patients with significant comorbidities, frailty or poor performance status that may prevent the use of chemotherapy.²⁸ Patients enrolled into the *RESONATE* trial were deemed to be inappropriate for re-treatment with purine analogues because of short-progression free interval from chemoimmunotherapy (<3 years), high comorbidity score and older age or presence of del(17p). The group had a median of 2–3 prior therapies with most previously receiving alkylating agents (91%), purine analogs (81%) and anti-CD20 monoclonal antibodies (92%). Significantly higher response rates were observed in the ibrutinib group (63% vs. 4%; OR 17.4; 95% CI, 8.1 to 37.30) with a longer median PFS (not reached after a median follow up of 9.4 months compared with a PFS of 8.4 months in the ofatumumab group). One year OS was also improved in the ibrutinib group (90% vs. 81%; HR for death 0.43 (95% CI, 0.24 to 0.79; P = 0.005)). The most frequent adverse events (20%) reported in the ibrutinib group were diarrhea, fatigue, pyrexia, and nausea compared with infusion-related reactions, cough and fatigue in the ofatumumab group. Serious adverse events were more common in the ibrutinib arm (81 (42%) vs. 58 (30%)) which was primarily due to a small increase in the incidence of cardiac events and atrial fibrillation (13 (7%) vs. 6 (3%)) and infections (46 (24%) vs. 39 (20%)).

Ibrutinib has also been studied as frontline therapy in untreated, older patients (> 65 years) in a phase 1b/2, open-label, multicenter trial.²⁹ In this trial patients were treated with ibrutinib at a dose of 420 mg (n=27) or 820 mg (n=4) daily. A partial or complete response was seen in 22/31 (71%, 95% CI 52.0–85.8); 4 patients (13%) achieved a CR. Of the remaining patients that did not achieve CR or PR, 4 (13%) achieved a PRL and 3 (10%) had stable disease. Interestingly, the median time to first response was 1.9 months (IQR 1.8–4.6) and the median time to complete response was 12.4 months (9.1–14.7), which are longer time intervals to response than would occur with conventional chemoimmunotherapy. The estimated 2 year PFS was 96.3% (95% CI 76.5–99.5) and 2 year OS was 96.6% (95% CI 77.9–99.5). Nine patients (31%) required a dose interruption due to an adverse event and two patients (7%) discontinued the medication due to an adverse event (reasons: grade 3 fatigue and grade 2 viral infection). The majority of adverse events were grade 1–2 with the

most five most frequently reported being: diarrhea (68%), nausea (48%), fatigue (32%), hypertension (29%) and peripheral edema (29%).

Obinutuzumab

Mechanism of action

CD20 is a transmembrane protein that is broadly expressed on both malignant and normal B-lymphocytes. The physiologic role of CD20 is incompletely understood and no endogenous ligand has been identified, although it appears to facilitate calcium influx during antigen recognition by the B-cell receptor and may play a role in T-cell independent antibody responses.^{30,31} Targeting of the CD20 molecule using monoclonal antibodies has markedly improved outcomes for multiple B-cell malignancies, including CLL.³² Antibodies targeting CD20 are often described as type I or type II which originates from a classification scheme developed during early work on these agents; type I antibodies cause CD20 to redistribute into detergent-resistant microdomains known as rafts, whereas type II antibodies do not cause this redistribution.³¹ The cytotoxic activity of type I antibodies is thought to largely depend on complement activation whereas type II antibodies appear to stimulate antibody-dependent cell-mediated cytotoxicity (ADCC).³¹ Rituximab and ofatumumab are both classified as type I antibodies and are widely used in CLL in combination with purine analogues and alkylating agents and as monotherapy, although they have modest efficacy as single agents. Obinutuzumab is a humanized type II IgG1 antibody that binds the same epitope as rituximab but has a unique glycoengineered Fc-region.³³ Pre-clinical data with obinutuzumab demonstrated increased direct and effector cell-dependent cytotoxicity with this agent compared with rituximab.^{33,34}

Summary of clinical trials

Obinutuzumab has been shown to have activity in CLL and B-cell lymphomas as a single agent³⁵⁻³⁷ and the final results of the phase I/2 GAUGUIN trial using single agent obinutuzumab in relapsed/refractory CLL have been recently reported.³⁵ Overall response rates at the completion of treatment for the phase I and 2 cohorts were 62% and 15% respectively; it was suggested by the authors that patients in the latter cohort had a higher burden of disease based on the sum of the 6 largest lymph nodes possibly explaining the difference in response rates. Infusion reactions occurred in almost all patients but the majority were low grade (1/2).

The efficacy of obinutuzumab in frontline treatment has been demonstrated in a recent randomized trial comparing 3 treatment arms: chlorambucil alone vs. chlorambucil + rituximab vs. chlorambucil + obinutuzumab.³⁸ The trial included patients with coexisting conditions as defined by a Cumulative Illness Rating Scale (CIRS) score of >6 and/or creatinine clearance (CrCl) < 70 mL/min. The rate of overall response and complete response was highest in the patients treated with obinutuzumab and chlorambucil. Interestingly, testing for minimal residual disease (MRD) was performed in a subset of patients (obinutuzumab, n=133; chlorambucil, n=114) and the rate of negativity was lower in the obinutuzumab group compared with rituximab group (bone marrow 19.5 vs. 2.6%). The addition of obinutuzumab significantly increased PFS compared with the other two groups

(median PFS: 26.7 months vs. 15.2 months (rituxumab + chlorambucil) vs. 11.1 months (Chlorambucil)). In a subgroup analysis this improvement in PFS appeared to extend to all subgroups except those with deletion 17p. Patients treated with chlorambucil and obinutuzumab had an OS advantage compared to those treated with chlorambucil alone (HR for death 0.41; 95% CI 0.23–0.74, $p=0.002$) although no significant OS difference was demonstrated between the rituximab and obinutuzumab containing groups. There was a higher incidence of infusion reactions and grade 3 and 4 neutropenia in the obinutuzumab group. Interestingly, there was also a small increase in tumor lysis syndrome with the use of obinutuzumab as compared with rituximab ($n=14$ (4%) vs. $n=0$).

Incorporating novel agents into clinical practice

Younger, fitter patients

Combination chemoimmunotherapy with fludarabine, cyclophosphamide and rituximab (FCR) is widely used as first line therapy in CLL for younger, fit patients requiring treatment. The CLL8 trial demonstrated a survival advantage for FCR over FC, reporting an ORR of approximately 90% with a CR rate of 35% with FCR.³⁹ The median PFS in CLL8 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 MD Anderson Cancer Center.^{39–41} Use of ibrutinib and other B-cell signaling inhibitors as frontline treatment of younger fitter patients has not been explored. In the phase 1b/2 trial of ibrutinib in untreated, older patients, rates of overall response and complete response appear to be lower than those reported in trials using FCR.²⁹ Despite this, the 2 year PFS and OS of 97 and 96% suggest that responses are durable, although the follow-up is short and the number of patients is small. A multi-center, randomized clinical trial is underway comparing FCR with ibrutinib and rituximab with a primary outcome of PFS and will explore the role of ibrutinib in this group of patients, although the preliminary results from this trial may not be available until 2016.⁴² Currently, FCR remains the standard of care for younger, fitter patients and ibrutinib is not approved for this indication.

Older patients and those with significant comorbidities

Ibrutinib, idelalisib/rituximab and chlorambucil/obinutuzumab are all potential treatment options for untreated older patients or those with significant comorbidities that are unsuitable for treatment with FCR, although only ibrutinib (for patients with 17p deletion) and obinutuzumab are currently approved by the FDA for this indication. It is challenging to provide specific recommendations about what constitutes optimal first-line treatment in this relatively heterogeneous group of patients as there have been few randomized comparisons between regimens. The combination of chlorambucil and obinutuzumab may improve response rate and PFS compared with chlorambucil and rituximab, but as there is no clear overall survival advantage some countries may be initially reluctant to adopt this due to concerns about cost. Ibrutinib represents a good treatment option in older, frail adults and can result in durable responses, although it is not approved for first-line treatment outside of patients with the 17p deletion. The potentially increased risk of atrial fibrillation with ibrutinib is a relevant concern in older patients and the mechanism underlying this is not well understood. The risk of bleeding with ibrutinib is also concerning for older patients

although the number of reported events was low in the phase II trial.²² Trials using ibrutinib have excluded patients on warfarin; yet the need for anticoagulation for indications such as atrial fibrillation, venous thromboembolism and valvular heart disease increases with age. Finally, we do not know how chlorambucil/obinutuzumab and ibrutinib compare with other more active chemotherapy regimens sometimes used in older, fit patients such as: bendamustine plus rituximab, fludarabine plus rituximab or dose reduced FCR. Ultimately clinicians must balance their own treatment expectations as well as the patients' with the anticipated toxicity of the treatment.

Relapsed disease

Currently, there is no standard of care for treatment of relapsed CLL and treatment decisions are usually based on prior therapy as well as individual patient characteristics and preferences. We expect that ibrutinib and idelalisib/rituximab will have an important role for the treatment of patients with relapsed disease requiring therapy, and we suggest that this is likely preferable to re-treatment with chemoimmunotherapy for most patients. In the relapsed setting, treatment with bendamustine/rituximab (BR) was reported to produce a PFS of 15.2 months (95% CI 12.5–17.9 months).⁴³ As well, median PFS after treatment with FCR in the relapsed setting has been reported to between 28–31 months.^{44,45} The use of ibrutinib and idelalisib/rituximab in the relapsed/refractory setting appears likely to produce a median PFS longer than what has been reported using either FCR or BR.^{12,22,46,47} Although it is challenging to compare the results of different studies, it appears that ibrutinib and idelalisib have better efficacy than chemoimmunotherapy in this setting with a relatively favorable side-effect profile. It is not known if combining these novel agents with chemoimmunotherapy might improve outcomes and survival in the treatment of relapsed CLL. The HELIOS trial assessed combining ibrutinib with chemoimmunotherapy in relapsed CLL and has completed enrollment⁴⁸; patients in this trial received 6 cycles of bendamustine and rituximab and were randomly assigned to receive ibrutinib 420 mg daily or placebo at the initiation of chemotherapy until disease progression. There is a similar ongoing phase 3 trial for patients with relapsed CLL treating with 6 cycles of bendamustine and rituximab and randomizing patients to either idelalisib 150 mg twice daily or placebo.⁴⁹

Higher Risk disease

Novel agents are potential treatment options for patients with higher risk disease such as those with deletion 17p, unmutated immunoglobulin variable region and rapid progression after initial treatment with purine-analogue containing regimens. Currently, for eligible patients with deletion 17p it has been suggested that treatment with allogeneic transplant be considered in CR1 or at first relapse as this a potentially curative option in patients with poor response to purine-analogue based chemotherapy and shortened survival.^{50,51} A recent study reporting outcomes in 52 patients with CLL and deletion 17p suggested inferior survival in patients not receiving an allogeneic transplant at the time of relapse with a 2 year OS of 25% compared with 64% in the transplant group (p=0.001).⁵² This trial was not randomized so it was subject to confounding factors; half of the non-transplanted group did not receive a transplant due to refractory disease or death during salvage therapy. A German transplant group described the outcomes of 90 patients with poor risk CLL receiving allogeneic transplant using a reduced intensity conditioning regimen; they reported a 4 year PFS of

42%, an OS of 65%, and a non-relapse mortality of 23%.⁵³ The risk associated with allogeneic transplant in CLL is not insignificant and in our experience many clinicians are reluctant to recommend transplant in first remission for this reason. We suggest that treatment with ibrutinib may be a good option for some patients with higher risk disease, as there appears to be activity in this population with the possibility of a durable response.^{29,46} Although the initial published results of ibrutinib in relapsed disease did not show a lower response rate for patients with 17p deletion, longer term follow-up shows that this group has a shorter PFS.⁴⁶ Despite this, follow-up of patients with relapsed disease and 17p deletion in the RESONATE trial reports a 1-year PFS of 79%, which suggests many patients in this high risk group may achieve a durable response.⁵⁴ However, it is still our practice to refer high risk patients with relapsed CLL responding to ibrutinib for a transplant assessment to discuss the risks and benefits of the procedure and assess eligibility.

Conclusions

The novel agents approved within the last year offer new treatment options that will improve outcomes for individuals with CLL. Many questions remain about their use including long-term efficacy, safety, and how and when to best incorporate these treatments into therapy. In addition to these agents, we anticipate that several other novel therapies including BCL-2 inhibitors, Akt inhibitors and 2nd generation BTK and PI3K δ inhibitors may be approved, expanding treatment options. The treatment paradigm with the B-cell signaling inhibitors is unique compared to conventional chemotherapy as patients are treated continuously until disease progression or intolerable side-effects. Responses with ibrutinib and idelalisib also appear to occur at a slower rate than chemoimmunotherapy, and many patients who experience only a partial response may have durable responses with long term disease control. Cost is an important factor for many individuals and countries and may prohibit the use of these agents. There may be also differences in the occurrence of late effects such as the development of secondary malignancies, including myelodysplastic syndrome and acute myeloid leukemia and Richter's transformation in patients treated with B-cell receptor inhibitors versus chemoimmunotherapy. Longer follow-up is required for this and to determine the long-term tolerability of these medications.

Acknowledgments

William G. Wierda **Research Funding:** AbbVie, Roche/Genentech. **Consultancy:** Roche/Genentech

Jan A. Burger **Research funding:** Gilead, Pharmacyclics

Susan M. O'Brien **Research funding:** Emergent, Genentech, Gilead Sciences, Infinity, MorphoSys, Pharmacyclics, Spectrum, Acerta, TG Therapeutics. **Consultancy:** Amgen, Celgene, Emergent, Genentech, Gilead Sciences, Infinity, Pharmacyclics, Spectrum

References

1. Duhren-von Minden M, Ubelhart R, Schneider D, et al. Chronic lymphocytic leukaemia is driven by antigen-independent cell-autonomous signalling. *Nature*. 2012; 489:309–312. [PubMed: 22885698]
2. Avalos AM, Meyer-Wentrup F, Ploegh HL. B-cell receptor signaling in lymphoid malignancies and autoimmunity. *Adv Immunol*. 2014; 123:1–49. [PubMed: 24840946]

3. Okkenhaug K, Bilancio A, Farjot G, et al. Impaired B and T cell antigen receptor signaling in p110delta PI 3-kinase mutant mice. *Science*. 2002; 297:1031–1034. [PubMed: 12130661]
4. Clayton E, Bardi G, Bell SE, et al. A crucial role for the p110delta subunit of phosphatidylinositol 3-kinase in B cell development and activation. *J Exp Med*. 2002; 196:753–763. [PubMed: 12235209]
5. Jou ST, Carpino N, Takahashi Y, et al. Essential, nonredundant role for the phosphoinositide 3-kinase p110delta in signaling by the B-cell receptor complex. *Mol Cell Biol*. 2002; 22:8580–8591. [PubMed: 12446777]
6. Cully M, You H, Levine AJ, et al. Beyond PTEN mutations: the PI3K pathway as an integrator of multiple inputs during tumorigenesis. *Nat Rev Cancer*. 2006; 6:184–192. [PubMed: 16453012]
7. Zou ZJ, Zhang R, Fan L, et al. Low expression level of phosphatase and tensin homolog deleted on chromosome ten predicts poor prognosis in chronic lymphocytic leukemia. *Leuk Lymphoma*. 2013; 54:1159–1164. [PubMed: 23013295]
8. Barragan M, Bellosillo B, Campas C, et al. Involvement of protein kinase C and phosphatidylinositol 3-kinase pathways in the survival of B-cell chronic lymphocytic leukemia cells. *Blood*. 2002; 99:2969–2976. [PubMed: 11929788]
9. Ringshausen I, Schneller F, Bogner C, et al. Constitutively activated phosphatidylinositol-3 kinase (PI-3K) is involved in the defect of apoptosis in B-CLL: association with protein kinase Cdelta. *Blood*. 2002; 100:3741–3748. [PubMed: 12393602]
10. Hoellenriegel J, Meadows SA, Sivina M, et al. The phosphoinositide 3'-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronic lymphocytic leukemia. *Blood*. 2011; 118:3603–3612. [PubMed: 21803855]
11. Lannutti BJ, Meadows SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. *Blood*. 2011; 117:591–594. [PubMed: 20959606]
12. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014; 123:3390–3397. [PubMed: 24615777]
13. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2014; 370:997–1007. [PubMed: 24450857]
14. Valiaho J, Smith CI, Vihinen M. BTKbase: the mutation database for X-linked agammaglobulinemia. *Hum Mutat*. 2006; 27:1209–1217. [PubMed: 16969761]
15. Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N Engl J Med*. 2011; 365:2497–2506. [PubMed: 22150006]
16. Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. *Nature*. 2011; 475:101–105. [PubMed: 21642962]
17. Herman SE, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood*. 2011; 117:6287–6296. [PubMed: 21422473]
18. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci U S A*. 2010; 107:13075–13080. [PubMed: 20615965]
19. Cheng S, Ma J, Guo A, et al. BTK inhibition targets in vivo CLL proliferation through its effects on B-cell receptor signaling activity. *Leukemia*. 2014; 28:649–657. [PubMed: 24270740]
20. Chang BY, Francesco M, De Rooij MF, et al. Egress of CD19(+)CD5(+) cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients. *Blood*. 2013; 122:2412–2424. [PubMed: 23940282]
21. Advani RH, Buggy JJ, Sharman JP, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol*. 2013; 31:88–94. [PubMed: 23045577]
22. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2013; 369:32–42. [PubMed: 23782158]
23. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic

- Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008; 111:5446–5456. [PubMed: 18216293]
24. Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia*. 2014; Published online 20 August 2014. doi: 10.1038/leu.2014.247
 25. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014; 370:2286–2294. [PubMed: 24869598]
 26. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014; 371:213–223. [PubMed: 24881631]
 27. Wierda WGKT, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, Robak T, Furman RR, Hillmen P, Trneny M, Dyer MJ, Padmanabhan S, Piotrowska M, Kozak T, Chan G, Davis R, Losic N, Wilms J, Russell CA, Osterborg A. Hx-CD20-406 Study Investigators. Ofatumumab As Single-Agent CD20 Immunotherapy in Fludarabine-Refractory Chronic Lymphocytic Leukemia. *J Clin Oncol*. 2010; 28:1749–1755. [PubMed: 20194866]
 28. Guidelines, N. NCCN Guidelines version 4.2104 CLL/SLL. National Comprehensive Cancer Network. 2014. Available at: <http://www.nccn.org/about/nhl.pdf>
 29. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. *Lancet Oncol*. 2014; 15:48–58. [PubMed: 24332241]
 30. Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. *J Clin Invest*. 2010; 120:214–222. [PubMed: 20038800]
 31. Beers SA, Chan CH, French RR, et al. CD20 as a target for therapeutic type I and II monoclonal antibodies. *Semin Hematol*. 2010; 47:107–114. [PubMed: 20350657]
 32. Maloney DG. Anti-CD20 antibody therapy for B-cell lymphomas. *N Engl J Med*. 2012; 366:2008–2016. [PubMed: 22621628]
 33. Mossner E, Brunker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood*. 2010; 115:4393–4402. [PubMed: 20194898]
 34. Alduaij W, Ivanov A, Honeychurch J, et al. Novel type II anti-CD20 monoclonal antibody (GA101) evokes homotypic adhesion and actin-dependent, lysosome-mediated cell death in B-cell malignancies. *Blood*. 2011; 117:4519–4529. [PubMed: 21378274]
 35. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood*. 2014; 124:2196–202. [PubMed: 25143487]
 36. Sehn LH, Assouline SE, Stewart DA, et al. A phase 1 study of obinutuzumab induction followed by 2 years of maintenance in patients with relapsed CD20-positive B-cell malignancies. *Blood*. 2012; 119:5118–5125. [PubMed: 22438256]
 37. Salles G, Morschhauser F, Lamy T, et al. Phase 1 study results of the type II glycoengineered humanized anti-CD20 monoclonal antibody obinutuzumab (GA101) in B-cell lymphoma patients. *Blood*. 2012; 119:5126–5132. [PubMed: 22431570]
 38. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014; 370:1101–1110. [PubMed: 24401022]
 39. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010; 376:1164–1174. [PubMed: 20888994]
 40. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood*. 2008; 112:975–980. [PubMed: 18411418]
 41. Fink AM, Böttcher S, Ritgen M, et al. Prediction of poor outcome in CLL patients following first-line treatment with fludarabine, cyclophosphamide and rituximab. *Leukemia*. 2013; 27:1949–1952. [PubMed: 23787395]
 42. Ibrutinib and Rituximab Compared With Fludarabine Phosphate, Cyclophosphamide, and Rituximab in Treating Patients With Untreated Chronic Lymphocytic Leukemia or Small

- Lymphocytic Lymphoma. ClinicalTrials.gov. 2014. Available at: <https://clinicaltrials.gov/ct2/show/NCT02048813>
43. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol.* 2011; 29:3559–3566. [PubMed: 21844497]
 44. Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol.* 2010; 28:1756–1765. [PubMed: 20194844]
 45. Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukemia. *J Clin Oncol.* 2005; 23:4070–4078. [PubMed: 15767647]
 46. O'Brien, SM.; Furman, R.; Coutre, SE., et al. Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease (abstract 7014). Presented at 2014 ASCO Annual Meeting; Chicago, USA. May 30–June 3; 2014.
 47. Brown, JR.; Hillmen, P.; O'Brien, SM., et al. Updated Efficacy Including Genetic and Clinical Subgroup Analysis and Overall Safety in the Phase 3 RESONATE™ Trial of Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (abstract 3331). Presented at 56th ASH Annual Meeting; San Francisco, USA. December 6–9; 2014.
 48. Hallek M, Kay NE, Osterborg A, et al. The HELIOS trial protocol: a Phase III study of ibrutinib in combination with bendamustine and rituximab in relapsed/refractory chronic lymphocytic leukemia. *Future Oncol.* 2014:1–9.
 49. Randomized, A. Double-Blind and Placebo-Controlled Study of Idelalisib in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia (NCT01569295). ClinicalTrials.gov. 2014. Available at: <https://clinicaltrials.gov/ct2/show/NCT01569295>
 50. Dreger P, Corradini P, Kimby E, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. *Leukemia.* 2007; 21:12–17. [PubMed: 17109028]
 51. Sellner L, Denzinger S, Dietrich S, et al. What do we do with chronic lymphocytic leukemia with 17p deletion? *Curr Hematol Malig Rep.* 2013; 8:81–90. [PubMed: 23188619]
 52. Poon ML, Fox PS, Samuels BI, et al. Allogeneic stem cell transplant in patients with chronic lymphocytic leukemia with 17p deletion: consult-transplant versus consult-no-transplant analysis. *Leuk Lymphoma.* 2014:1–5.
 53. Dreger P, Dohner H, Ritgen M, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. *Blood.* 2010; 116:2438–2447. [PubMed: 20595516]
 54. O'Brien, S.; J, J.; Coutre, S.; Mato, AR.; Hillmen, P.; Tam, C.; Osterborg, A.; Siddiqi, T.; Thirman, MJ.; Furman, RF.; Ilhan, O.; Keating, M.; Call, TG.; Brown, JR.; Stevens-Brogan, M.; Li, Y.; Fardis, M.; Clow, F.; James, DF.; Chu, AD.; Hallek, M.; Stilgenbauer, S. Efficacy and Safety of Ibrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Leukemia with 17p Deletion: Results from the Phase II RESONATE-17 Trial (abstract 327). Presented at the 56th ASH Annual Meeting; San Francisco, USA. December 6–9; 2014.
 55. Redbook. Truven Health Analytics Inc; 2014. Available at: <http://sites.truvenhealth.com/redbook/index.html>

Table 1

Summary of published clinical trials in CLL

Trial	Patient group (n)	Treatments	Response rate - % (CR/* PR)	OS (PFS)
<i>Ibrutinib</i>				
Byrd et al ²²	Relapsed/Refractory CLL/SLL (n=85)	Ibrutinib 420 – 840 mg/day	ORR 71 (2/98)	26 month OS: 83% (26 month PFS: 75%)
O'Brien et al ²⁹	Untreated CLL/SLL, Age 65. (n=31)	Ibrutinib 420–840 mg/day	ORR 71 (13/87)	2 year OS: 97% (2 year PFS: 96%)
Byrd et al ²⁶	Relapsed/Refractory CLL/SLL (n=196)	<i>Open label RCT:</i> Ibrutinib 420 mg/day vs. Ofatumumab 300 mg × 1 dose, then 2000 mg × 11 dose	Ibrutinib ORR 63 (0/100); Ofatumumab ORR 4 (0/100)	1 year OS: Ibrutinib 91% vs. Ofatumumab 81% (6 month PFS: Ibrutinib 88% vs. Ofatumumab 65%)
<i>Idelalisib</i>				
Brown et al ¹²	Relapsed/Refractory CLL/SLL (n=54)	Idelalisib 50 mg bid up to 350 mg bid	ORR 72 (0/100)	3 year OS: ~75% (median PFS 15.8 months)
Furman et al ¹³	Relapsed/Refractory CLL/SLL ineligible for cytotoxic therapy (n=220)	<i>Double blind RCT:</i> Rituximab × 8 doses + Idelalisib 150 mg bid (R+I) vs. Rituximab × 8 doses + placebo (R)	R+I: ORR 81 (0/100), R: ORR 13 (0/100)	1 year OS: R+I 92% vs. R 80%. (24 week PFS: R+I 93% vs. R 46%)
<i>Obinutuzumab</i>				
GAUGUIN Phase 1 Cartron et al ³⁵	Relapsed/Refractory CLL (n=13)	Obinutuzumab 400 – 2000 mg × 8 doses	ORR 62 (0/100)	Not reported
GAUGUIN Phase 2 Cartron et al ³⁵	Relapsed/Refractory CLL (n=20)	Obinutuzumab 400 – 2000 mg × 10 doses	ORR 15 (0/100)	Median PFS: 10.7 months
Goede et al ³⁸	Untreated CLL, patients with comorbid conditions (n=781)	<i>Open label RCT:</i> (1) Chlorambucil (C) vs. (2) Chlorambucil + Ritux (C+R) vs. (3) Chlorambucil + Obinutuzumab (C+O)	C: ORR 31 (0/100) C+R: ORR 65 (11/89) C+O: OR 77 (29/71) **	No OS between C +R and C+O; HR 0.66; 95% CI, 0.41 to 1.06; p = 0.08, (Median PFS: C+R 15.2 months vs. C +O 26.7 months)

* Partial response (PR) includes partial response with lymphocytosis

** Response rates are for 1st comparison

Table 2

Basic prescribing information for novel agents

Drug	FDA Approval for CLL	Dose	Approximate cost per treatment*	Commonly Reported Side effects
Obinutuzumab	Approved in combination with chlorambucil in previously untreated CLL	100 mg day 1, Cycle 1 900 mg day 2, Cycle 1 1000 mg day 8 and 15, Cycle 1 1000 mg day 1, Cycles 2–6	\$50,000	Infusion - reactions, neutropenia, (cases of tumor lysis reported)
Idelalisib	Relapsed CLL in combination with rituximab specifically for patients where rituximab monotherapy would be considered appropriate due to comorbidities	150 mg bid	\$105,000 (\$139,000 including rituximab)	Diarrhea, colitis, nausea, fatigue, hypertension, edema, pneumonitis, elevated liver enzymes
Ibrutinib	Approved as monotherapy in patients with CLL and at least one prior treatment, and as frontline therapy in patients with deletion 17p	420 mg/day**	\$128,000	Diarrhea, cough, rash, arthralgia, fatigue

* Obinutuzumab cost calculated for 8 cycles. Ibrutinib and idelalisib cost calculated for 1 year course. Drug costs were calculated using drug pricing information from Redbook.⁵⁵

** Recommended dose for mantle cell lymphoma is 560 mg/day

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript